BMJ Open

The tuberculosis care cascade in Zambia: identifying the gaps in order to improve outcomes

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044867
Article Type:	Original research
Date Submitted by the Author:	16-Sep-2020
Complete List of Authors:	Lungu, Patrick; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia; University of Zambia University Teaching Hospital, Department of Internal Medicine Kerkhoff, Andrew; University of California San Francisco, ; San Francisco General Hospital and Trauma Center, Kasapo, Clara; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Mzyece, Judith; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Nyimbili, Sulani; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Chimzizi, Rhehab; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Kagujje, Mary; Center for Infectious Disease Research in Zambia Subbaraman, Ramnath; Tufts University School of Medicine, Department of Public Health and Community Medicine Muyoyeta, Monde ; Center for Infectious Disease Research in Zambia Malama, Kennedy; The Zambian Ministry of Health Silumesi, Andrew; Ministry of health Zambia
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The tuberculosis care cascade in Zambia: identifying the gaps in order to improve outcomes

Short title: TB Care Cascade in Zambia

AUTHORS: Patrick Lungu[1,2*], Andrew D. Kerkhoff[3*], Clara C. Kasapo[1], Judith Mzyece[1], Sulani Nyimbili[1], Rhehab Chimzizi[1], Andrew Silumesi[4], Mary Kagujje[5], Ramnath Subbaraman[6], Monde Muyoyeta[5], Kennedy Malama[4]

Affiliations:

[1]National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia
[2]Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia
[3]Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco, San Francisco, CA, USA
[4]Ministry of Health, Lusaka, Zambia
[5]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia
[6]Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, USA

*PL and ADK contributed equally.

Corresponding author:
Dr. Andrew Kerkhoff, MD, PhD
Email: Andrew.Kerkhoff@ucsf.edu

Article type: Original article

Keywords: Tuberculosis, care cascade, loss to follow-up, Zambia, HIV, rifampicin resistance

Abstract

Background: Tuberculosis (TB) remains a leading cause of morbidity and mortality among individuals in Zambia, especially people living with HIV (PLHIV). We undertook a care cascade analysis to identify the largest gaps and align TB program improvement measures with areas of greatest need.

Methods: We derived national-level estimates for each step of the care cascade for individuals with active TB disease in Zambia in 2018. We characterized the overall cascade as well as disaggregated by drug-susceptibility results and HIV-status. Estimates were informed by WHO incidence estimates, nationally aggregated laboratory and notification registers, and individual-level program data from four out of the country's ten provinces.

Results: In 2018, the total burden of TB in Zambia was estimated to be 72,495 (range, 40,495-111,495) cases. Of these, 43,387 (59.8%) accessed TB testing, 40,175 (proportion in relation to total TB burden – 55.4%, relative proportion in relation to previous step – 92.6%) were diagnosed with TB, 36,431 (50.3%, 90.7%) were started on TB treatment and 32,689 (45.1%, 89.7%) completed TB treatment. PLHIV tended to have worse outcomes throughout the cascade and were less likely than HIV-negative individuals to successfully complete TB treatment (42.8% vs. 50.2%). Among those with rifampicin-resistant TB, there was substantial attrition at each step of the cascade and only 22.1% of all patients were estimated to have successfully completed treatment.

Conclusions: Losses throughout the TB care cascade resulted in a large proportion of individuals with TB not successfully completing treatment. Ongoing health systems strengthening is required at every step of the care cascade; however, scale-up of active case finding strategies is particularly critical to ensure individuals with TB in the population reach initial stages of care. In addition, a renewed focus on PLHIV and individuals with drug-resistant TB is urgently needed to improve TB-related outcomes in Zambia.

Strengths and limitations of this study

- The national tuberculosis (TB) care cascade for Zambia in 2018 was characterized in order to identify the largest gaps in the care continuum.
- The TB care cascade was constructed for all TB patients as well as according to drug-susceptibility result and HIV-status.
- The analysis was informed by a published set of methodologies and utilized several data sources to derive estimates.
- Enhanced TB surveillance programs, including the use of unique TB patient identifiers, would allow for real-time monitoring and improved estimates to inform programmatic strengthening.

Background

The WHO End TB strategy aims to reduce incident tuberculosis (TB) cases by 90% and TB-related deaths by 95% between 2015 and 2035 [1]. While many high burden countries in sub-Saharan Africa, including Zambia have demonstrated large reductions in new TB cases and associated mortality, there remains significant need for improved TB control [2]. TB remains a leading cause of morbidity and mortality in Zambia, especially among people living with HIV (PLHIV) [3,4]. In 2018, there were approximately 60,000 new TB cases in Zambia (incidence rate 346 cases per 100,000 people) that resulted in 18,000 TB-related deaths, of which 72% were among PLHIV [4].

The HIV "cascade of care" outlines the series of steps that PLHIV go through in order be diagnosed with HIV, initiated on antiretroviral therapy (ART) and ultimately achieve an undetectable viral load. This model has been widely applied by HIV programs globally to inform and strengthen HIV care and delivery and ultimately, significantly increase the number of PLHIV who know their HIV status, are started on ART and have suppressed viral loads [5]. Similarly, a national TB care cascade can provide key insight to identify the largest gaps in the diagnosis and care of TB patients that could then help guide programmatic and research priorities by aligning limited resources with the areas of greatest need [6,7]. Despite their potential to help achieve improved TB-related outcomes and control, to date, only South Africa and India have undertaken and published national-level TB cascade of care analyses [8,9].

We sought to construct a national TB cascade of care for Zambia to evaluate national TB care delivery for individuals with active TB disease through enumeration of gaps in the overall care cascade in 2018 as well as disaggregated by rifampicin-susceptibility results and HIV-status. Estimates were derived using multiple data sources and the overall approach was informed by a recently published methodology for constructing TB care cascades [7].

Methods

Setting

Zambia has an estimated population of 18,400,000 people living in its Provinces [10]. It has a high prevalence of HIV (11.5% among adults aged 15-49 years old), and it estimated that at least 1.2 million persons are living with HIV [11]. TB is a major public health problem in Zambia [3]; during the last national TB prevalence survey conducted in 2013 and 2014, the prevalence of microbiologically-confirmed TB was estimated to be 638 per 100,000 persons and was five-times higher among HIV-positive individuals compared to HIV-negative individuals [12].

Testing and treatment for TB is almost universally provided within Zambia's public health system; while exact estimates are not available, a very small number of TB cases are detected and managed within Zambia's private sector. Within the public health sector, the direct costs of all TB diagnostics and treatment are provided free of charge. In 2018, Xpert MTB/RIF was the recommended first-line diagnostic for all individuals undergoing evaluation for possible TB (pulmonary or extra-pulmonary) in Zambia as well as initial drug-susceptibility testing (DST) [13]; however, it was not universally available at all facilities, in which case routine TB investigations included acid fast bacilli (AFB) fluorescence or Ziehl-Neelsen microscopy and chest radiography, where available. Among those with confirmed rifampicin-resistant (RR) or multi-drug resistant (MDR) TB, it was recommended that either liquid culture or a molecular line probe assay was used as follow-on tests for further DST [13]. First line TB treatment was provided to all patients without evidence of rifampicin-resistance and consisted of isoniazid, rifampicin, ethambutol and pyrazinamide for 6-9 months in conformity with WHO recommendations [14]. In 2018, Zambia began scaling up shorter treatment regimens comprised of new and repurposed TB drugs for 9-12 months for eligible RR- and MDR-TB patients – this accounted for the majority of cases [15,16]; however, some patients still received longer MDR-TB treatment regimens comprised of several TB drugs, including an injectable agent, for at least 20 months.

Patients diagnosed with TB are notified in a paper-based register and initiated on TB therapy at the corresponding TB treatment facility, which is also responsible for documentation of the treatment outcome of the patient. Data on diagnostic outcomes, notifications and treatment outcomes are aggregated from each facility through the district office to the national level on a monthly basis.

Ethics

Because this was a retrospective, population-level analysis without the use of any patient identifiers, this analysis did not qualify as human-subjects research and therefore was exempt from review by the University of Zambia Biomedical Research Ethics Committee.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this analysis. However, there are plans to disseminate the findings to TB communities through TB stakeholder meetings with neighborhood health committees, which includes former TB patients and other community TB advocates.

TB Cascade Data Sources

Several data sources were used to inform estimates within each step of the care cascade and these are clearly noted whenever relevant in the detailed data analysis approach (**Supplementary Appendix**). To inform estimates of the overall burden of TB in Zambia in 2018, WHO estimates of TB incidence from 2018 and 2017 were utilized [2,4,17]**.** The proportion of total TB cases estimated to be rifampicin-resistant was derived using estimates from the most recent national survey of TB drug resistance in Zambia [18]. Diagnostic outcomes were informed by a nationally aggregated database of TB diagnostics, which includes the number and type of investigations (Xpert or smear microscopy), by year as well as the number of TB cases detected according to type of TB investigation and HIV-status. All treatment outcomes were informed by a nationally aggregated TB treatment register. In Zambia all patients initiated on TB therapy have their outcome documented in a paper-based register at the corresponding TB treatment facility, which is then aggregated from each facility through the district office to the national level on a monthly basis. Individual level programmatic data from four Zambian Provinces (Eastern, Lusaka, Southern, Western) regarding all patients investigated for TB and those started on treatment between January 1st and December 31st 2017 (n=43,896, n=11,814, respectively) was used to estimate the proportion of patients who had both positive Xpert and smear microscopy results as well as the proportion of patients who were Xpert or smear-negative, but received empirical TB therapy. Sensitivity estimates stratified by HIV-status of Xpert [19] and smear microscopy [20,21] for the detection of TB as well as Xpert [19], molecular line probe assays

[22] and liquid culture [23] for rifampicin-resistance were informed by previously published systematic reviews and meta-analyses.

Estimation Methods

We calculated national-level estimates for each step of the TB care cascade in Zambia in 2018. This included: Step 1: The total TB burden (prevalent TB cases in 2018); Step 2: the total number who accessed TB testing; Step 3: the total number who were diagnosed with TB; Step 4: the total number who were notified and started on TB treatment; Step 5: the total number who successfully completed TB treatment. Each step of the cascade as well as the overall TB care cascade was calculated among all patients and disaggregated according to rifampicin-resistance result and among those with drug-susceptible TB, by HIV-status. Rifampicin resistant TB was defined as the detection of rifampicin resistance on any clinical specimen using Xpert, molecular line probe assay or liquid culture. Drug susceptible (DS) TB was defined as any TB case without known rifampicin resistance.

The approach to all estimates followed recommendations outlined in a published set of methods for constructing national-level TB care cascades [7]. Below, we describe a brief overview of the approach to calculate the TB care cascade, however, a highly detailed summary of all assumptions, calculations, estimates, and data sources is summarized in **Supplementary Tables 1-5**. We first started with Step 4 (the total number of patients who were notified and started on TB treatment - including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases [24]) and Step 5 (the total number who successfully completed TB treatment), which were both directly informed by aggregated facility-level notification data. Step 3 (the total number who were diagnosed with TB) was then back calculated from the number of cases notified (Step 4) and the proportion of patients who were estimated to have been lost-to-follow-up prior to initiation of TB therapy (pre-treatment loss-to-follow-up [PTLTFU]); PTLTFU was estimated based on the difference between the number of microbiologically-confirmed DS pulmonary TB cases that were detected in 2018 (informed by aggregated facility-level laboratory data) and the number of all microbiologically-confirmed DS pulmonary TB cases that were notified (informed by aggregated facility-level notification data). Step 2 (the total number who accessed TB testing) was calculated by adding the number of

cases missed due to the incomplete sensitivity of TB diagnostic assays to the number of total TB cases diagnosed (Step 3). The overall approach for Steps 2-5 was similar for both DS-TB and RR-TB (**Supplementary Tables 1-5**). The overall TB burden (all forms) was estimated using the WHO TB incidence estimate for 2018, plus 50% of the number all cases that remained undiagnosed in 2017; a 50% estimate has previously been utilized and assumed that the remaining 50% of undiagnosed cases in 2017 either self-cured or died [9,25]. To determine the total number of rifampicin resistant TB cases (Step 1), we multiplied the overall TB burden by the proportion of all patients who had rifampicin resistance detected during a national drug resistance survey [18]. The total number DS-TB cases was calculated using the total TB burden minus the number of RR-TB cases. All "gaps" between each step were calculated by taking the difference in the total number of cases and uncertainty estimate (either 95% confidence intervals or range) between the succeeding and proceeding step. All TB care cascades were depicted graphically using bar charts representing the absolute number of cases and associated uncertainty measurement (if applicable). For each step of each cascade, proportions relative the total TB burden (Step 1) as well as relative to the prior step were calculated.

To understand any progress that may have underpinned the 2018 TB care cascade, we also evaluated TB diagnostic and treatment completion trends from 2015 to 2018. Using facility-level aggregated laboratory data, the number of Xpert tests sent each year were plotted against (a) the total number of pulmonary TB cases diagnosed each year, including the proportion that was microbiologically confirmed as well as (b) the total number of RR-TB cases diagnosed and notified each year. We also plotted the proportion of TB patients each year who started TB treatment that successfully completed it, disaggregated according to TB case type: (1) HIV-positive new/relapse pulmonary TB, (2) HIV-negative new/relapse pulmonary TB, (3) retreatment TB not including relapse cases, (4) extrapulmonary TB, (5) RR-TB.

Results

Overall National TB Care Cascade for 2018

In 2018, the overall burden of TB in Zambia was estimated to be 72,495 cases (range: 40,495-111,495; **Table 1; Figure 1a**). Of the total burden of TB cases, 43,387 (59.8%) were estimated

to have sought care for their TB illness and undergone microbiologic TB testing. Among these individuals 40,175 (overall proportion - 55.4%, relative proportion 92.6%) were diagnosed with TB, 36,431 (overall proportion – 50.3%, relative proportion 90.7%) were notified and initiated on TB therapy and 32,689 (overall proportion – 45.1%, relative proportion 89.7%) completed TB therapy. Therefore, 39,806 (54.9%) of the estimated TB cases in 2018 did not complete the TB care cascade. Individuals who did not seek care for their TB illness or who sought care but did not undergo microbiological TB testing accounted for 29,108 (73.1%) TB cases lost along the cascade in 2018 (**Table 2)**; incomplete diagnostic sensitivity among individuals accessing microbiologic testing contributed to an additional 3,211 (8.1%) missed TB cases, and losses-to-follow-up prior to TB treatment initiation and prior to TB treatment completion accounted for 3,745 (9.4%) and 3,742 (9.4%) cases lost, respectively.

TB Care Cascade by Drug Susceptibility Result

We estimated the burden of drug susceptible (DS) TB in 2018 to be 70,755 (range, 40,009-107,481) cases - approximately 97.6% of the total TB burden. The DS-TB cascade was largely similar to the overall TB cascade with 32,304 (45.7%) of all cases being diagnosed with TB, initiating on and completing TB treatment (**Table 1; Figure 1b)**. The total number of rifampicin-resistant (RR) TB cases was estimated to be 1,740 (range, 486-4,014), or 2.4% of the total TB burden. Compared to DS-TB cases, individuals with RR-TB were substantially less likely to access microbiological TB testing (52.3% vs. 60.0%, p<0.001), have their TB diagnosed (68.9% vs. 93.1%, p<0.001), be notified and initiated on TB treatment (81.2% vs. 90.8%, p<0.001) and to complete TB therapy (75.6% vs. 89.9%, p<0.001) (**Figure 1c)**. Thus, only 385 (22.1%) RR-TB cases completed the TB care cascade. The majority RR-TB cases along the pathways were due to individuals who did not seek care or who did not have access to TB and/or drug susceptibility testing (61.3%; **Table 2**); however, 283 (20.9%) of lost RR-TB cases were among those who accessed TB testing and had RR-TB missed, 118 (8.7%) were among those who had RR-TB detected but were not notified and started on appropriate TB therapy, and 124 (9.2%) were among those who did not complete RR-TB therapy (**Table 2**).

Drug Susceptible TB Care Cascade by HIV-status

Of 70,755 drug-susceptible TB cases in 2018, 43,411 (range, 23,911-65,911; 61.4%) were estimated to be among people living with HIV, while 27,344 (range, 16,098-41,570; 38.6%) were estimated among those who were HIV-negative. Compared to patients with DS-TB who were HIV-negative, HIV-positive patients with DS-TB were less likely to access microbiological TB testing (57.0 vs. 64.8%) and were less likely to complete TB treatment (88.4% vs. 92.1%). This resulted in a lower overall proportion of HIV-positive patients compared to HIV-negative patients completing the TB care cascade (42.8% vs. 50.2%, p<0.001; **Table 1; Figures 1d and 1e**). For both HIV-positive and HIV-negative patients with DS-TB, the largest loss in the care cascade was due to patients not accessing microbiological TB testing resulting in 18,597 (75.2%) and 10,939 (70.6%) missed cases, respectively.

TB Diagnosis Trends from 2015 to 2018

Between 2015 and 2018 Xpert MTB/RIF was increasingly utilized as the first-line TB diagnostic tool in Zambia where 24,140 Xpert tests were sent for suspected pulmonary TB in 2015, which increased to 163,470 sent in 2018 (**Figure 2a**). During this same period, the number of sputum AFB smear microscopy investigations decreased from 95,300 in 2015 to 25,323 in 2018. While there was a small decrease in the absolute number of pulmonary TB cases diagnosed and notified in 2018 compared to 2015 (31,272 vs. 33,452), the proportion of microbiologically-confirmed TB cases that were notified during that period, substantially increased (56.0% [95CI, 55.5-56.6] vs. 44.1% [95%CI, 43.6-44.7]; **Figure 2a**). The scale-up of Xpert testing between 2015 and 2018 was also associated with a more than three-fold increase in the annual number of RR cases detected (627 vs. 196), and more than five-fold increase in the annual number of rifampicin resistant TB cases that were notified and started on appropriate TB treatment (509 vs. 99; **Figure 2b**). During this period, there was corresponding reduction in the proportion of PTLTFU RR-TB cases from 49.5% in 2015 to 18.8% in 2018 (p<0.001).

TB Treatment Completion Trends from 2015 to 2018

Finally, we examined trends in the proportion of DS-TB patients who completed TB treatment once they were notified and initiated on therapy (**Figure 3**). Among new/relapse pulmonary TB cases, treatment completion rates steadily increased between 2015 and 2018 (86.2 vs. 90.3%,

p<0.001); potentially improved TB treatment outcomes were seen among both retreatment pulmonary TB cases (84.4% vs. 87.2%, p=0.06). From 2015 to 2018, the proportion of patients with extrapulmonary TB completing TB treatment also improved (80.6% vs. 87.8%, p<0.001). The proportion of HIV-positive patients completing TB therapy remained relatively unchanged (87.3% vs. 88.4%, p=0.001), while incremental improvements were seen among patients who had a negative or unknown HIV-status (82.4% vs. 91.8%, p<0.001) (**Figure 3**); in 2018, a slightly lower proportion of HIV-positive TB patients completed therapy compared to HIV-negative patients (difference 3.4%, p<0.001). Differences in treatment outcomes according to HIV-status were driven by a higher absolute number and proportion of cases that died or were LTFU during treatment among HIV-positive individuals compared to those who were HIV-negative (**Supplementary Table 1).**

Discussion

In this study we found that less than half of all TB cases in Zambia in 2018 were diagnosed with TB, initiated on TB treatment and completed therapy. We identified important losses at each step of the TB care cascade, however, we estimate that more than 40% of all individuals with TB in Zambia are not accessing microbiological TB testing. These results highlight important research and programmatic priorities for improving TB care and TB-related outcomes in Zambia.

This represents the third national TB care cascade that has been characterized from a high burden TB country and builds upon similar analyses from South Africa and India [8,9]. Our overall TB care cascade results are similar to those from both countries that found that only about 50% of all TB patients were progressing through all steps of the care cascade and completing TB treatment. In India the largest losses in the care cascade were among those who did not access TB testing (28% of all cases) [8], while in South Africa steady losses were seen prior to TB diagnosis (12% of all cases), prior to starting TB treatment (13% of all cases) and prior to successful completion of TB therapy (17% of all cases) [9]. In Zambia, 40% were estimated to have not accessed TB testing, while 4-5% of all TB cases were lost at each subsequent step of the care cascade. These differences highlight specific programmatic needs at different steps within the TB care cascade for each country and provides insight into the unique challenges that they each face.

Our results are consistent with several TB prevalence surveys suggesting that a large proportion of individuals with TB face barriers to healthcare seeking, barriers to accessing microbiological TB testing, or both [26,27]. Unfortunately, we are not able to discern whether the estimated 40% gap in patients not accessing TB microbiological investigations is predominantly driven by (a) individuals who fundamentally lacked access to primary health and TB facilities, (b) individuals who either delayed or never presented to TB testing facilities for evaluation of their illness, or (c) is due to individuals who sought care at health facilities, but their illness was not suspected to be TB and thus they never had TB testing undertaken [28]. This has been shown to be a common problem in recent standardized patient studies conducted in Kenya [29], India [30] , and China [31]. In the last Zambian national TB prevalence survey conducted in from 2013 to 2014, only 60% of previously undiagnosed TB cases were symptomatic, of which 50% had sought care for their illness at a health facility [12]. This suggests that both community-based and facility-based active TB case finding strategies, as well as training of healthcare providers to improve recognition of and testing for TB, are likely to be important to TB control activities in Zambia. Community-based active TB case finding may help overcome individuals' barriers to health-seeking and accessing TB services, possibly resulting in a greater absolute number of TB cases diagnosed and cases that are detected earlier [32,33]; when implemented broadly, this may reduce community TB prevalence [34]. However, effective and sustainable community-based active TB case finding strategies are not well-described and represent an urgent TB research need [27,35]. There is strong evidence demonstrating that facility-based, active TB case finding strategies are efficient and may yield a large number of cases that would otherwise have been missed, especially in high burden settings [36,37]. A recent implementation science study evaluating a multicomponent active TB case finding in a high burden primary health care facility in Lusaka, Zambia found that total TB notifications increased by 35% during the intervention period (from 247 to 394 cases per 100,000 population); of the total TB cases, 91.5% were from facility-based case finding interventions while 8.5% were from community-based case finding interventions [38].

We estimate that nearly 10% of individuals diagnosed with TB were lost from follow-up prior to initiation of TB treatment. Pre-treatment losses to follow-up are common in many high-burden

settings as demonstrated by a systematic review that found that 4-38% (weighted proportion 18%) of TB patients in sub-Saharan Africa were lost at this step in the cascade [39]. This may be accounted for by patients who died prior to initiation of therapy – a common finding among such patients – and patients who cannot be traced after diagnosis either due to missing/incorrect contact information, or because they have moved away. However, pre-treatment loss-to-follow-up estimates also fail to account for individuals who were in fact started on TB therapy, but were not officially registered and therefore never notified to the national TB program (NTP). Zambia's NTP has recently completed a study to estimate the proportion of patients who are diagnosed but not notified as well as the proportion of those who are started on treatment but never reported. This study will yield improved estimates of pre-treatment loss-to-follow-up, which will allow for improved evaluations of programmatic changes that aim to improve TB diagnosis and linkage to TB treatment and care.

We found that important progress has been made in Zambia with regard to microbiological TB diagnosis and TB treatment completion from 2015 to 2018. During this period there was a massive effort to scale-up the availability of Xpert MTB/RIF as the first-line TB diagnostic for all forms of TB. This was associated with a 12% increase in the proportion of TB cases that were microbiologically-confirmed (2,692 additional annual drug-susceptibility cases). Importantly, because Xpert also provides rapid simultaneous detection of rifampicin-resistance, its scale-up was also associated with a three-fold increase in RR-TB cases detected and a five-fold increase in the number of RR-TB cases that were notified and started on TB treatment. Zambia is currently preparing to scale-up Xpert Ultra cartridges, which when paired with continued efforts to decentralize Xpert testing, should allow for further gains in the detection of HIV-associated TB, extra-pulmonary TB, and RR-TB [40]. There was also evidence of improved TB treatment completion rates for nearly all forms of TB between 2015 and 2018. While it is important to recognize progress that has been made, important gaps in the TB care continuum remain due to missed diagnoses and lack of treatment completion. Further efforts to expand access to microbiological TB testing and interventions to bolster TB treatment adherence and retention in care are needed [41].

PLHIV accounted for more than 60% of TB cases and Zambia and that they were more likely to be lost at several steps of the cascade compared to HIV-negative individuals. This emphasizes the need for increased HIV-TB collaborative activities [42]. Due to non-specific clinical presentations and radiographic findings, one of the most important challenges to improving HIV-associated TB outcomes remains TB diagnosis [43]. Non-specific symptoms may delay care-seeking among PLHIV, and without systematic TB screening among PLHIV presenting to and in-care, the diagnosis of many TB cases may be further delayed or missed. Systematic screening for TB at each clinical presentation [44] must be coupled with access to improved microbiological diagnostic tools such as Xpert Ultra [45] and urine LAM [45,46] testing to facilitate rapid TB detection and TB treatment initiation in order to minimize pre-treatment loss-to and improve clinical outcomes. Compared to HIV-negative patients, HIV-positive patients were less likely to complete TB therapy, and TB treatment completion rates among PLHIV did not significantly change over a four-year period from 2015 to 2018. Previously, a study among PLHIV in Zambia found that a large number of individuals LTFU from HIV services had died and that programmatic mortality rates were substantially under-reported [47]; this suggests that mortality among PLHIV LTFU from TB treatment services is high and that TB-related mortality among PLHIV in Zambia is likely underestimated. The implementation of tailored interventions to improve adherence to TB treatment [41,48] as well as antiretroviral therapy [49] among this highly vulnerable population therapy are needed.

Notably, we found that less than one quarter of rifampicin resistant TB cases in 2018 were detected, started on appropriate treatment and completed appropriate therapy. This was despite improved access to rapid drug susceptibility via the scale-up of Xpert MTB/RIF testing from 2015 to 2018 and shorter and simplified drug-resistant TB regimens being introduced in 2018 [15]. The high rate of attrition of rifampicin-resistant TB patients throughout the care cascade argues for the need for specific investments in systems strengthening to improve drug resistant TB diagnosis and treatment in Zambia, mirroring this dire need in most high TB burden countries [4,27,50,51]. One important contributing factor to the large number of RR-TB patients not accessing DST is the high proportion of patients who are being diagnosed clinically and/or on the basis of radiological findings only – this accounted for approximately 44% of pulmonary TB cases in Zambia in 2018. Notably, the scale-up of Xpert testing between 2015 to 2018 was

associated with a more than 30% reduction in the proportion of RR-/MDR-TB cases that were lost-to-follow-up after diagnosis and prior to initiation of treatment – this is likely due to the substantially faster detection of rifampicin resistance compared to conventional culture-based methods. Collectively, this demonstrates the importance of continued efforts to expand access to Xpert testing in Zambia in order to facilitate confirmation of TB diagnoses coupled with rapid detection of rifampicin resistance. While the implementation of existing diagnostic tools as well as improved DR-TB treatment regimens must be optimized, there remains an urgent need for the development of rapid low-cost drug susceptibility testing (DST) that can be scaled-up to provide decentralized access to first and second-line DST aligned with current treatment recommendations [52], as well as continued progress towards shorter, less toxic, and more effective DR-TB treatment regimens [53]. Additionally, the last national drug resistance survey was conducted in 2008 [18]. An updated drug resistance survey is currently underway and will provide new estimates that will better guide programmatic priorities.

This study utilized a validated analysis method [7] incorporating a number of data sources to derive nationally representative estimates of the TB care cascade in Zambia, however there were some limitations. As with other published TB cascades analyses, there is uncertainty around the estimates, especially the overall number of TB cases. The total burden of TB was calculated using indirect estimates from modelling that were based upon case notification data and a prior national TB prevalence survey. We derived a conservative estimate of the total TB burden that accounted for missed cases from the prior year [9] and that therefore may be a more appropriate estimate than measurements of TB incidence, which are rarely feasible to directly estimate [54]. Due to a lack of a unique national patient identifier, we were unable to link individual patient outcomes as they progressed through the TB care cascade; where possible, we attempted to account for duplicate diagnostic and treatment data, which was uncommon. Implementation of a unique TB patient identifier, and an improved TB data surveillance program with enhanced data integration would greatly improve future estimates and allow for real time individual-level, facility-level, and sub-national-level data to inform program strengthening. Furthermore, this analysis utilizes data from public health facilities. The overall contribution of the private health sector to TB diagnosis and treatment in Zambia is estimated to be negligible; thus, this is not likely to substantially bias our estimates. Zambia's NTP is currently endeavoring

to quantify the proportion of cases diagnosed and treated in the private sector and to improve private sector engagement. Finally, to our knowledge, there are no locally or regionally-representative estimates of TB relapse rates after documented TB treatment completion. This is an important quality metric of individuals' adherence to therapy as well as TB treatment programs and should be assessed in future research studies [7].

In conclusion, in 2018 only 45% of all TB cases in Zambia completed the TB care cascade, and most losses were among patients who never accessed TB testing. Additionally, only 22% of all RR-TB patients successfully completed appropriate TB treatment and HIV-positive patients had substantially worse TB outcomes compared HIV-negative patients. Our results suggest that continued systems-strengthening is required throughout the TB care continuum, however, implementation of active TB case finding strategies coupled with a renewed focus on those with rifampicin-resistance and PLHIV are urgently needed to improve TB-related outcomes and TB control in Zambia.

Contributions

PL, ADK and MM conceived the study. CCK, JM, and SN collected and organized the data. ADK conducted the analysis and developed the figures with input from PL, MM, CCK, JM, SN and RS. ADK, PL, and MM wrote the first draft of the manuscript. All authors contributed to interpretation of data and editing of the article and approved the final version of the manuscript before submission.

Funding

ADK was supported by the National Institute of Allergy and Infectious Diseases (Grant No T32 AI060530).

Disclaimer

The funding sources had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the manuscript for publication.

Data availability statement

All data relevant to this study are included in the article or uploaded as supplementary information.

Competing Interests

All authors declare no competing interests.

References

1 WHO. The End TB Strategy. World Health Organization, Geneva; 2015.

2 WHO. World Health Organization. Global Tuberculosis Report 2018. World Health Organization, Geneva; 2019.

3 CDC. CDC in Zambia. Center for Disease Control and Prevention, Atlanta; 2017.

4 World Health Organization. Global Tuberculosis Report 2019. World Health Organization, Geneva; 2020.

5 Medland NA, McMahon JH, Chow EP, *et al.* The HIV care cascade: a systematic review of data sources, methodology and comparability. *J Int AIDS Soc* 2015;**18**:20634. doi:10.7448/ias.18.1.20634

6 Reid MJA, Goosby E. Lessons learned from the HIV care cascade can help End TB. *Int J Tuberc Lung Dis* 2017;**21**:245–6. doi:10.5588/ijtld.17.0027

7 Subbaraman R, Nathavitharana RR, Mayer KH, *et al.* Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLOS Med* 2019;**16**:e1002754-18. doi:10.1371/journal.pmed.1002754

8 Subbaraman R, Nathavitharana RR, Satyanarayana S, *et al.* The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002149-38. doi:10.1371/journal.pmed.1002149

9 Naidoo P, Theron G, Rangaka MX, *et al.* The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. *J Infect Dis* 2017;**216**:S702–13. doi:10.1093/infdis/jix335

10 UNFPA. Zambia - Overview. United Nations Population Fund, Geneva; 2020.

11 UNAIDS. Country factsheets - Zambia 2019. Joint United Nations Programme on HIV/AIDS, Geneva; 2020.

12 Kapata N, Chanda-Kapata P, Ngosa W, *et al.* The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. *PLOS ONE* 2016;**11**:e0146392-14. doi:10.1371/journal.pone.0146392

13 The National Tuberculosis and Leprosy Program. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in Zambia. 2017

14 WHO. Guidelines for treatment of drug-susceptible tuberculosis and patient care. World Health Organization, Geneva; 2017.

15 Challenge TB. Rapid Scale-Up of New Drugs and Regimens for the Treatment of Drug-Resistant TB in Zambia. FHI 360 Zambia Office, Lusaka 2020.

16 Zambia Ministry of Health. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection: 2018.

17 P Glaziou, C Sismanidis, PJ Dodd, M Zignol, K Floyd. Methods used by WHO to estimate the global burden of TB disease. World Health Organization, Geneva; 2018.

18 Kapata N, Mbulo G, Cobelens F, *et al.* The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health* 2015;**20**:1492–500. doi:10.1111/tmi.12581

19 Horne DJ, Kohli M, Zifodya JS, *et al.* Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev* Published Online First: 2019. doi:10.1002/14651858.cd009593.pub4

20 Boehme CC, Nicol MP, Nabeta P, *et al.* Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011;**377**:1495–505. doi:10.1016/s0140

21 Steingart KR, Henry M, Ng V, *et al.* Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006;**6**:570–81. doi:10.1016/s1473-3099(06)70578-3

22 WHO. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. World Health Organization, Geneva; 2016.

23 Tortoli E, Benedetti M, Fontanelli A, *et al.* Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *Journal of Clinical Microbiology* 2002;**40**:607–10. doi:10.1128/jcm.40.2.607-610.2002

24 WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization, Genevea; 2014. n.d.

25 Dye C. Breaking the law: tuberculosis disobeys Styblo's rule. *B World Health Organ* 2008;**86**:4–4. doi:10.2471/blt.07.049510

26 Horton KC, MacPherson P, Houben RMGJ, *et al.* Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002119. doi:10.1371/journal.pmed.1002119

27 Reid MJA, Arinaminpathy N, Bloom A, *et al.* Building a tuberculosis-free world: The Lancet Commission on tuberculosis. *Lancet* 2019;**393**:1331–84. doi:10.1016/s0140-6736(19)30024-8

28 Subbaraman R, Jhaveri T, Nathavitharana RR. Closing gaps in the tuberculosis care cascade: an action-oriented research agenda. *J Clin Tuberc Other Mycobact Dis* 2020;**19**:100144. doi:10.1016/j.jctube.2020.100144

29 Daniels B, Dolinger A, Bedoya G, *et al.* Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. *BMJ Glob Health* 2017;**2**:e000333. doi:10.1136/bmjgh-2017-000333

30 Kwan A, Daniels B, Saria V, *et al.* Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. *POS Med* 2018;**15**:e1002653. doi:10.1371/journal.pmed.1002653

31 Sylvia S, Xue H, Zhou C, *et al.* Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. *PLOS Med* 2017;**14**:e1002405. doi:10.1371/journal.pmed.1002405

32 Kranzer K, Afnan-Holmes H, Tomlin K, *et al.* The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013;**17**:432–46. doi:10.5588/ijtld.12.0743

33 STOP TB Partnership. Finding the Missing People with TB in Communities. Stop TB Partnership, Geneva; 2018.

34 Marks GB, Nguyen NV, Nguyen PTB, *et al.* Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New Engl J Med* 2019;**381**:1347–57. doi:10.1056/nejmoa1902129

35 Kerkhoff AD, Muyoyeta M, Cattamanchi A. Community-wide Screening for Tuberculosis. *New Engl J Med* 2020;**382**:1185–6. doi:10.1056/nejmc1916666

36 Shapiro AE, Chakravorty R, Akande T, Lonnroth K , Golub JE. A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. World Health Organization, Geneva; 2013.

37 STOP TB Partnership. Intensified TB Case Finding at Facility Level. Stop TB Partnership, Geneva; 2018.

38 Kagujje M, Chilikutu L, Somwe P, *et al.* Active TB case finding in a high burden setting; comparison of community and facility-based strategies in Lusaka, Zambia. *PLOS ONE* 2020.

39 MacPherson P, Houben RM, Glynn JR, *et al.* Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *B World Health Organ* 2013;**92**:126–38. doi:10.2471/blt.13.124800

40 Dorman SE, Schumacher SG, Alland D, *et al.* Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis* 2018;**18**:76–84. doi:10.1016/s1473-3099(17)30691-6

41 Alipanah N, Jarlsberg L, Miller C, *et al.* Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLOS Med* 2018;**15**:e1002595. doi:10.1371/journal.pmed.1002595

42 WHO. WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. World Health Organization, Geneva; 2012.

43 Kerkhoff AD, Cattamanchi A. HIV and Tuberculosis. 2019;:127–59. doi:10.1007/978-3-030-29108-2_7

44 WHO. Systematic screening for active tuberculosis: principles and recommendations. World Health Organization, Geneva; 2013.

45 WHO. WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. World Health Organization, Geneva; 2017.

46 WHO. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019. World Health Organization, Geneva; 2019.

47 Holmes CB, Sikazwe I, Sikombe K, *et al.* Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. *PLOS Med* 2018;**15**:e1002489. doi:10.1371/journal.pmed.1002489

48 Subbaraman R, Mondesert L de, Musiimenta A, *et al.* Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *BMJ Glob Health* 2018;**3**:e001018. doi:10.1136/bmjgh-2018-001018

49 Kanters S, Park JJH, Chan K, *et al.* Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017;**4**:e31–40. doi:10.1016/s2352-3018(16)30206-5

50 Dowdy DW, Theron G, Tornheim JA, *et al.* Drug-resistant tuberculosis in 2017: at a crossroads. *Lancet Respir Med* 2017;**5**:241–2. doi:10.1016/s2213-2600(17)30081-4

51 Dheda K, MD PTG, MMed PGM, *et al.* The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med* 2017;**5**:291–360. doi:10.1016/s2213-2600(17)30079-6

52 WHO. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. World Health Organization, Geneva; 2014.

53 Kendall EA, Sahu S, Pai M, *et al.* What will it take to eliminate drug-resistant tuberculosis? *Int J Tuberc Lung Dis* 2019;**23**:535–46. doi:10.5588/ijtld.18.0217

54 Stop TB Partnership. TB Impact Measurement. Stop TB Partnership, Geneva; 2012.

Figure Legend

Figure 1. The tuberculosis care cascade in Zambia in 2018 among: (a) all tuberculosis cases; (b) drug-susceptible cases; (c) rifampicin-resistant cases; (d) drug-susceptible cases among HIV-positive individuals; (e) drug-susceptible cases among HIV-negative individuals**.**

Figure 2. Diagnoses and notifications of (a) all forms of drug-susceptible pulmonary tuberculosis in Zambia between 2015 and 2018, and (b) drug-resistant tuberculosis in Zambia between 2015 and 2018.

Figure 3. Overview of drug-susceptible tuberculosis treatment outcomes in Zambia between 2015 and 2018, disaggregated according to tuberculosis-type. Shapes represent the proportion of patients completing tuberculosis treatment.

Supporting information

Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV-status.

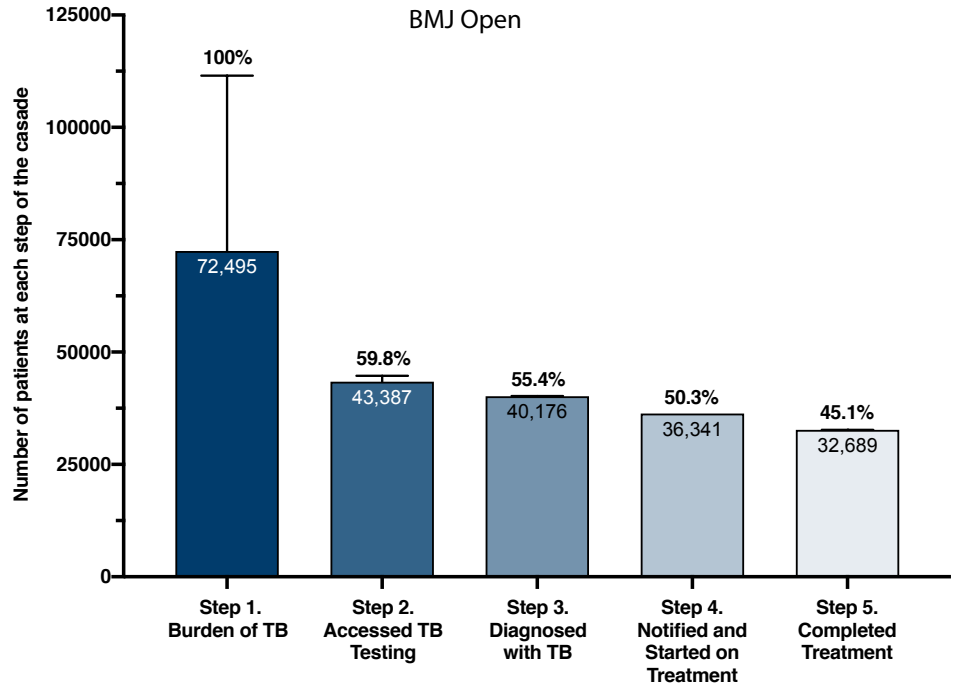
Table 1. Overview of the tuberculosis care cascade in Zambia in 2018 according to type of TB

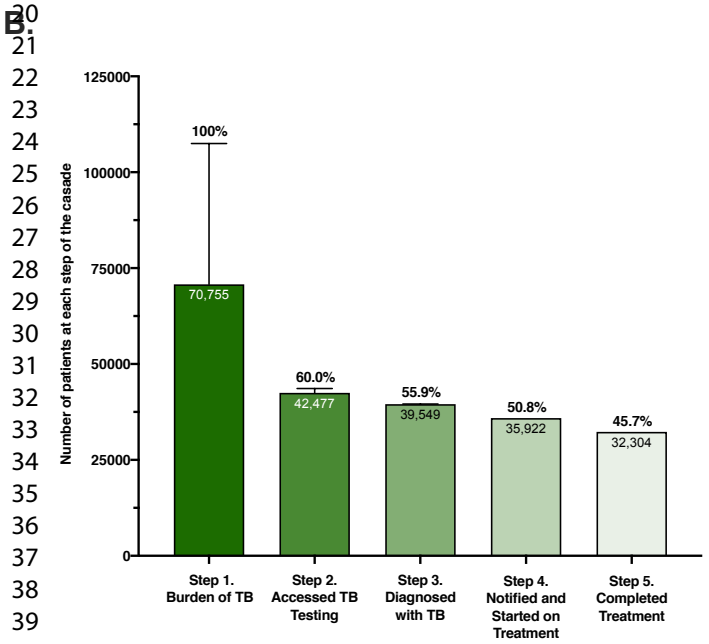
	Step 1. TB burden		Step 2. Accessed tests			Step 3. Diagnosed			Step 4. Notified and treated			Step 5. Successfully treated		
	Cases, range	Proportion (%)	Cases, range	Proportion (%)		Cases, range	Proportion (%)		Cases, range	Proportion (%)		Cases, range	Proportion (%)	
Overall TB Cascade	72,495 (40,495-111,495)	100	43,387 (95%CI: 42,390-44,710)	59.8	59.8	40,176 (95%CI: 40,128-40,212)	55.4	92.6	36,431	50.3	90.7	32,689 (95%CI: 32,662-32,713)	45.1	89.7
Rifampin-resistant TB	1,740 (486-4,014)	100	910 (95%CI: 776-1,093)	52.3	52.3	627	36.0	68.9	509	29.3	81.2	385 (95%CI: 358-409)	22.1	75.6
DS-TB, all	70,755 (40,009-107,481)	100	42,477 (95%CI: 41,614-43,625)	60.0	60.0	39,549 (95%CI: 39,501-39,585)	55.9	93.1	35,922	50.8	90.8	32,304	45.7	89.9
DS-TB, HIV-positive	43,411 (23,911-65,911)	100	24,746 (95%CI: 24,290-25,349)	57.0	57.0	23,133 (95%CI: 23,106-23,154)	53.3	93.5	21,012 (95%CI: 20,962-21,064)	48.4	90.8	18,579 (95%CI: 18,535-18,625)	42.8	88.4
DS-TB, HIV-negative	27,344 (16,098-41,570)	100	17,731 (95%CI: 17,324-18,276)	64.8	64.8	16,415 (95%CI: 16,395-16,431)	60.0	92.6	14,910 (95%CI: 14,858-14,960)	54.5	90.8	13,725 (95%CI: 13,679-13,769)	50.2	92.1

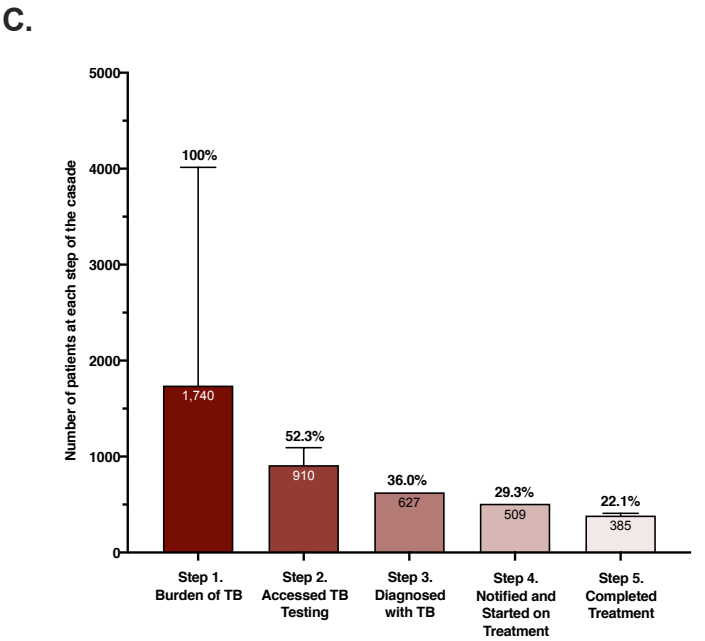
Table 2. Gap analysis of the tuberculosis care cascade in Zambia in 2018.

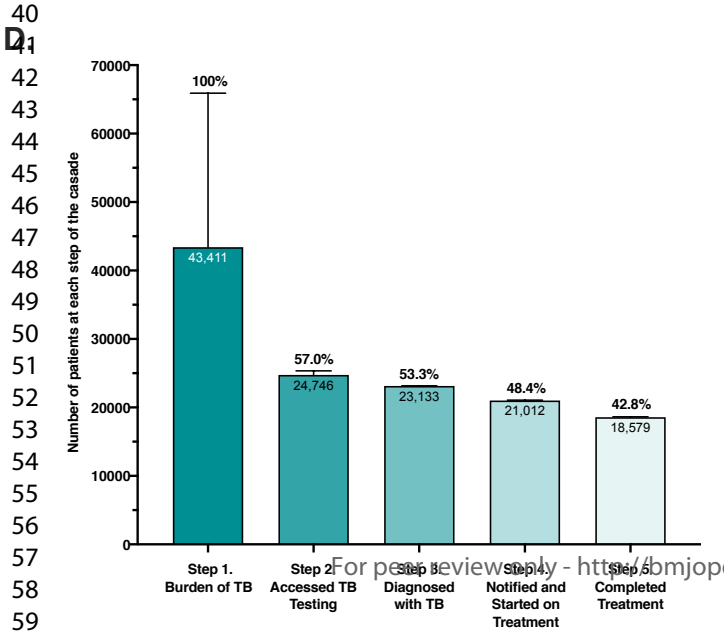
	Overall TB cases lost throughout the care cascade		Gap 1. Patient did not seek care at TB facility and/or have TB tests sent		Gap 2. TB tests sent, but TB missed*		Gap 3. TB diagnosed but patient not started on TB treatment and/or not notified		Gap 4. TB treatment started, but not completed	
	Cases, range	Proportion (%)	Cases, range	Proportion (%)	Cases, range	Proportion (%)	Cases, range	Proportion (%)	Cases, range	Proportion (%)
Overall TB Cascade	39,806 (7,833-78,782)	100	29,108 (0-66,777)	73.1	3,211 (95%CI: 2,262-4,506)	8.1	3,745 (95%CI: 3,697-3,781)	9.4	3,742 (95%CI: 3,718-3,769)	9.4
Rifampin-resistant TB	1,355 (128-3,605)	100	830 (0-2,921)	61.3	283 (95%CI: 149-466)	20.9	118	8.7	124 (95%CI: 100-151)	9.2
Drug-sensitive TB	38,451 (40,009-107,481)	100	28,278 (0-63,856)	73.5	2,928 (95%CI: 2,112-4,040)	7.6	3,627 (95%CI: 3,579-3,663)	9.4	3,618	9.4
HIV-positive, drug-sensitive TB	24,832 (5,376-47,286)	100	18,597 (0-40,495)	75.2	1,613 (95%CI: 1,185-2,194)	6.5	2,121 (95%CI: 2,094-2,142)	8.5	2,379 (95%CI: 2,337-2,529)	9.8
HIV-negative, drug-sensitive TB	13,619 (2,419-27,801)	100	10,939 (98-24,620)	70.6	1,315 (95%CI: 927-1,846)	9.7	1,505 (95%CI: 1,486-1,520)	11.1	1,239 (95%CI: 1,089-1,281)	8.7

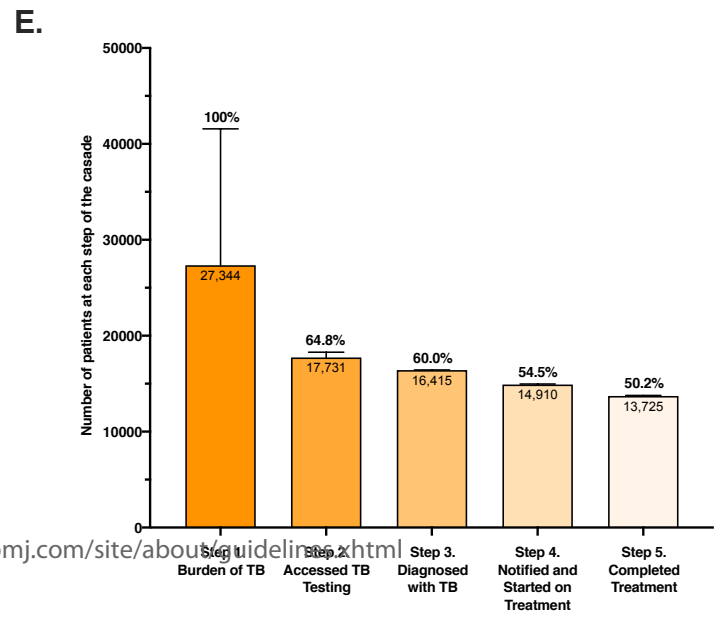
Proportions are relative to the total number of TB cases lost throughout the care cascade. *For rifampicin resistant TB, either the TB diagnosis or the rifampicin resistance was missed.



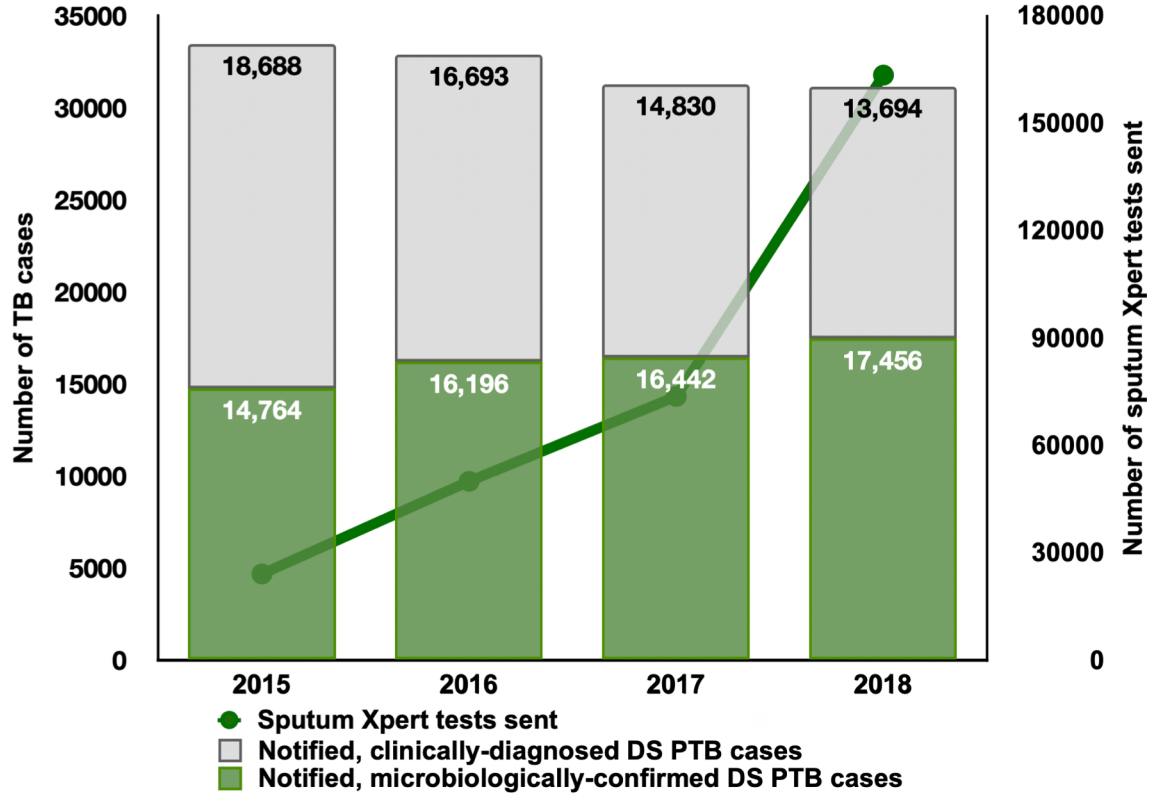




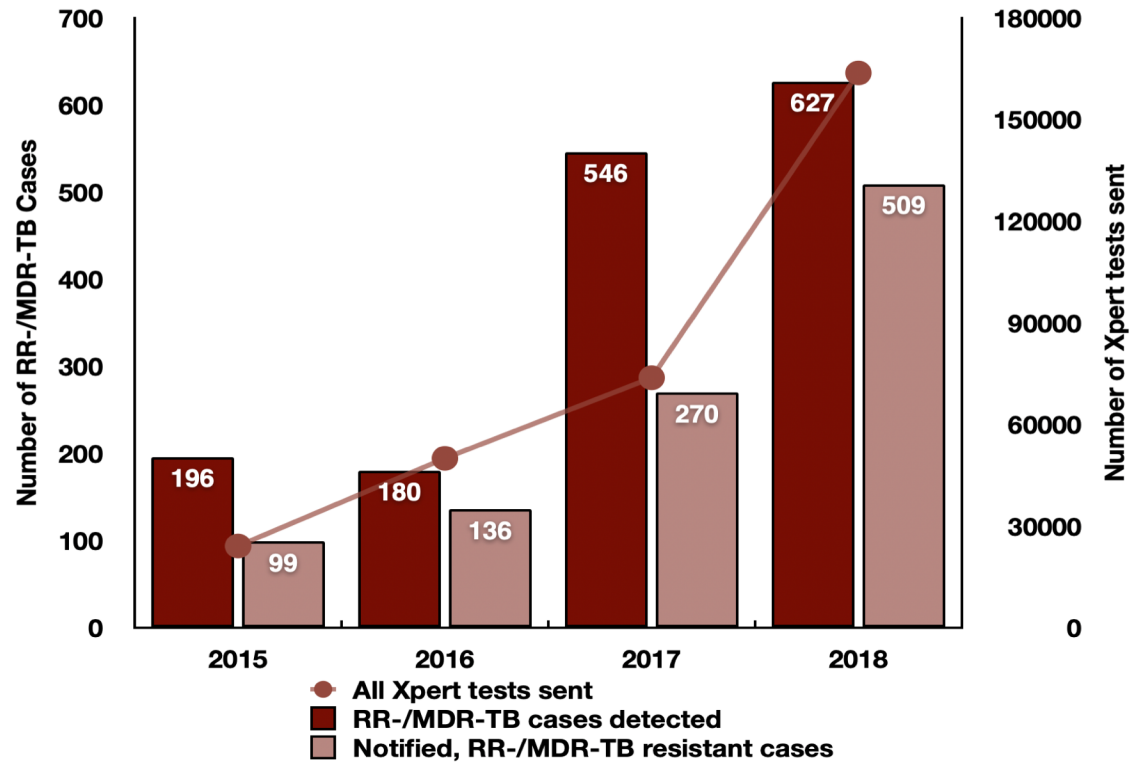


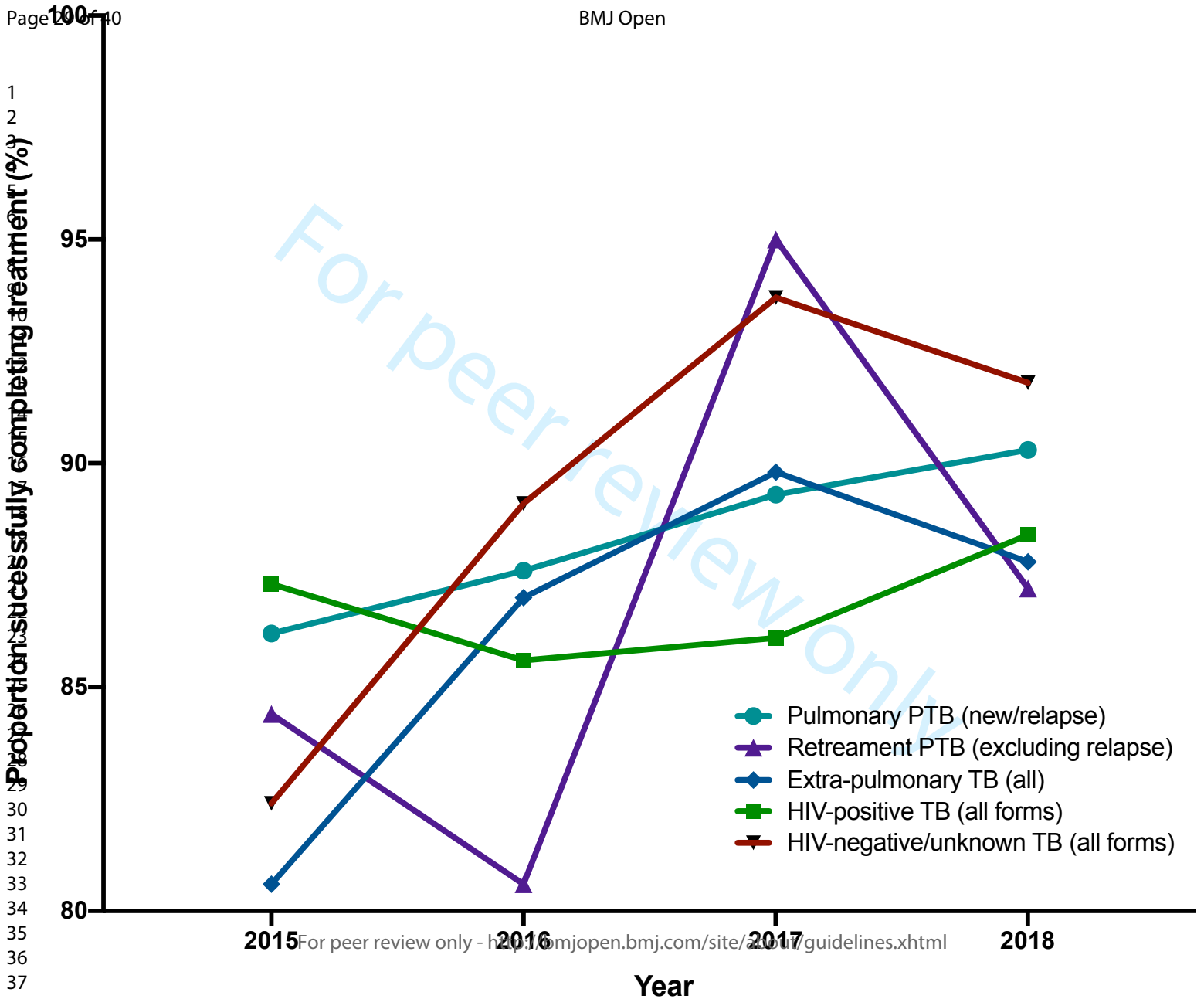


A.


35000
30000
25000
20000
15000
10000
5000
0
Number of TB cases
180000
150000
120000
90000
60000
30000
0
Number of sputum Xpert tests sent
18,688
16,693
14,830
13,694
14,764
16,196
16,442
17,456
2015
2016
2017
2018
Sputum Xpert tests sent
Notified, clinically-diagnosed DS PTB cases
Notified, microbiologically-confirmed DS PTB cases

B.


700
600
500
400
300
200
100
0
Number of RR-/MDR-TB Cases
180000
150000
120000
90000
60000
30000
0
Number of Xpert tests sent
196
99
180
136
546
270
627
509
2015
2016
2017
2018
All Xpert tests sent
RR-/MDR-TB cases detected
Notified, RR-/MDR-TB resistant cases



Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV-status.

	HIV-positive						HIV-negative or unknown HIV status					
	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated
2015	20967	18312 (87.3)	71 (0.3)	1117 (5.3)	682 (3.3)	785 (3.7)	20621	16986 (82.4)	102 (0.5)	1392 (6.8)	1168 (5.7)	973 (4.7)
2016	21655	18541 (85.6)	171 (0.8)	1354 (6.3)	705 (3.3)	884 (4.1)	18498	16481 (89.1)	55 (0.3)	1058 (5.7)	486 (2.6)	418 (2.3)
2017	20362	17527 (86.1)	136 (0.7)	1622 (8.0)	731 (3.6)	346 (1.7)	16841	15779 (93.7)	40 (0.2)	569 (3.4)	135 (0.8)	318 (1.9)
2018	19932	17624 (88.4)	113 (0.6)	1253 (6.3)	521 (2.6)	421 (2.1)	15990	14680 (91.8)	46 (0.3)	745 (4.7)	342 (2.1)	177 (1.1)

Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Table 1. Overall TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. TB burden	72,495 (40,495- 111,495)	100	WHO 2019 analysis of TB incidence in 2018 plus 50% of the number of undetected cases from 2017.	• TB incidence, 2018 (all): 60,000 • TB incidence, 2017 (all): 61,000 • Case detection rate, 2017: 59.0% • Estimated undetected cases 2017: 24,990 • 50% of undetected cases who have not died/self-cured: 12,495
Gap 1	29,108 (0-66,777)	40.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	43,387 (95%CI: 42,390-44,710)	59.8	Add DS TB and RR TB cases tested (see below for estimates)	• DS TB: 42,477 (95%CI: 41,614-43,625) • RR TB: 910 (95%CI: 776-1,093)
Gap 2	3,211 (95%CI: 2,262-4,506)	4.4	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed	40,176 (95%CI: 40,128- 40,212)	55.4	Add DS TB and RR cases diagnosed (see below for estimates)	• DS TB: 39,549 (95%CI: 39,501-39,585) • RR TB: 627
Gap 3	3,745 (95%CI: 3,697-3,781)	5.2	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated	36,431	50.3	Add DS TB and RR cases notified and treated (see below for estimates)	• DS TB: 35,922 • RR TB: 509
Gap 4	3,742 (95%CI: 3,718-3,769)	5.2	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated	32,689 (95%CI: 32,662-32,713)	45.1	Add DS TB and RR cases successfully treated (see below for estimates)	• DS TB: 32,304 • RR TB: 385 (95%CI: 358-409)

Table 2a. Drug-susceptible TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	70,755 (40,009-107481)	100	Overall TB burden minus DR TB cases.	• TB burden: 72,495 (40,495-111,495) • RR cases: 1740 (486-4014)
Gap 1	28,278 (0-63,856)	40.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	42,477 (95%CI: 41,614-43,625)	60.0	Add the number of missed cases to the total number of DS TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV-status, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b)	• Number diagnosed: 39,549 (95%CI: 39,501-39,585) • Number missed: 2,928 (95%CI: 2,112-4,040)
Gap 2	2,928 (95%CI: 2,112-4,040)	4.1	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	39,549 (95%CI: 39,501-39,585)	55.9	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy. PTLTFU estimated based on difference between number of microbiologically confirmed DS PTB cases detected and number of microbiologically confirmed DS PTB cases notified (Table 2c)	• PTLTFU estimate: = 9.2 (95%CI: 9.1-9.3) • Number of patients notified in 2018: 35,922
Gap 3	3,627 (95%CI: 3,579-3,663)	5.1	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	35,922	50.8	Aggregated facility-level TB notification data	• All patients with DS-TB who were notified and started on treatment (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).
Gap 4	3,618	5.1	Step 4 estimated cases minus Step 5 estimated cases	
Step 5. Successfully treated for TB.	32,304	45.7	Aggregated facility-level TB treatment outcomes data.	• All patients with DS-TB who successfully completed TB therapy (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).

Table 2b. Estimation method for determining number of patients with DS TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall
Total number of all microbiologically-confirmed TB cases (who therefore underwent microbiological tests)[1]	8,025 (PTB) + 320 (EPTB) = 8,345	9,803 (PTB)+1,137 (EPTB) = 10,940	19,285
Number of the above who underwent Xpert[1]	7,320	9,071	16,391
Number who underwent smear[1]	1,025	1,869	2,894
Proportion who underwent smear only (were smear-positive but Xpert either not done, or negative)[2]	96.9% (95%CI: 95.6-98.0)	98.1% (95%CI: 97.1-98.8)	97.7% (95%CI:96.9-98.3)
Number who underwent smear only	1,025 x .969% (95%CI: .956-.980) = 993 (95%CI: 980-1,005)	1,869 x .981% (95%CI: .971-.988) = 1,833 (95%CI: 1815-1,847)	-
Sensitivity of Xpert[3]	81% (95%CI 75-86)	88% (95%CI: 83-92)	85% (95%CI: 82-88)
Cases missed by Xpert	7,320/ .81 (95%CI .75-.86) - 7,320 = 1,717 (95CI: 1,192-2,440)	9,071 /.88 (95%CI: .83-.92)- 9,071 = 1,237 (95%CI: 789-1,858)	2,594 (95%CI: 1,980-4,298)
Sensitivity of smear microscopy[4,5]	50% (95%CI:42-57)	76% (95%CI: 70-80)	-
Cases missed by smear	993/0.50 (95%CI:0.42-0.57)- 993 = 1,025 (95%CI: 773-1,415)	1,833/0.76 (0.70-0.80)-1,833 = 590 (95%CI: 467-801)	1,615 (95%CI: 1,240-2,216)
Total combined cases missed by Xpert and smear	2,472 (95CI: 1,965-3,855)	1,827 (95%CI: 1,256-2,659)	4,569 (95%CI: 3,221-6,514)
Proportion of patients who had a negative Xpert that were empirically treated[2]	30.6% (95%CI: 28.6-32.7)	22.7% (95%CI:19.8-25.9)	28.9 (95%CI: 27.2-30.6)
Negative Xpert / received empiric therapy	1,717 (95CI: 1,192-2,440) x .306 (95%CI: .286-.327) = 525 (95: 341-798)	1,237 (95%CI: 789-1,858) x .227 (95%CI:.198-259) = 281 (95%CI: 156-481)	806 (95%CI: 497-1,279)

Proportion of patients who had a negative smear that were empirically treated[2]	58.9% (95%CI: 56.8-61.0)	39.2% (95%CI: 36.9-41.4)	50.1 (95%CI 48.5-51.6)
Negative smear / received empiric therapy	1,025 (95%CI: 773-1,415) x .589 (95%CI: .568-.610) = 604 (95%CI: 439-863)	590 (95%CI: 467-801) x .392% (95%CI: .369-.414) = 231 (95%CI: 172-332)	835 (95%CI: 612-1,195)
Total cases that were negative by Xpert or smear that were empirically treated	1,129 (95%CI: 780-1,661)	529 (95%CI: 329-813)	1,641 (95%CI: 1,109-2,474)
Total Missed cases (Total number of cases missed by Xpert or smear minus those were empirically treated)	1,613 (95%CI: 1,185-2,194)	1,315 (95%CI: 927-1,8460	2,928 (95%CI: 2,112-4,040)

[1]Exact value from national TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces (unpublished), [3]Esimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593.[4]Estimate from: Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 377:1495–505. [5]Estimate from: Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:570–81.

Table 2c. Estimation method for determining proportion of patients with pre-treatment lost-to-follow-up.

Variable	Overall
Unadjusted number of microbiologically-confirmed pulmonary TB cases[1]	19,285 (16,391 Xpert and 2,894 smear)
Proportion of patients with positive smear who also have a positive Xpert result[2]	2.3% (95%CI 1.7-3.1)
Number of patients with positive smear who also have a positive Xpert result[2]	2,894 x .023% (95%CI .017-.031) = 67 (95%CI: 49-90)
Adjusted number of microbiologically-confirmed PTB cases	(2,894 - 67 (95%CI: 49-90)) + 19,218 (95%CI: 19,195-19,236)
Number of patients with microbiologically-confirmed pulmonary TB notified in 2018[3]	17,456
Proportion of all patients with microbiologically-confirmed TB who were registered and started TB treatment	90.8 (95%CI: 90.7-90.9)
Pre-treatment lost-to-follow-up (PTLTFU) estimate:	100% - 90.8 (95%CI: 90.7-90.9) = 9.2% (95%CI: 9.1-9.3)

[1]Exact value from nationally aggregated TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces (unpublished).[3]Exact value from nationally aggregated TB notification register

Table 3. Rifampicin resistant TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	1,740 (486-4,014)	100	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance.	• TB burden: 72,495 (40,495-111,495) • Overall estimate of RR TB: 2.4% (95CI: 1.2-3.6)[1]
Gap 1	830 (range, 0-2,921)	47.7	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	910 (95%CI: 776-1,093)	52.3	Back calculated from RR tuberculosis cases diagnosed on the basis of cases bacteriologically diagnosed, by test type and test sensitivity	• RR TB cases diagnosed: 627 • RR TB cases missed: 283
Gap 2	283 (95%CI: 149-466)	16.3	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	627	36.0	Aggregated facility-level TB laboratory data	• All patients with microbiologically-confirmed RR-TB
Gap 3	118	6.8	Step 3 estimated cases minus Step 4 estimated cases	
Step 4. Notified and treated for TB	509	25.3	Aggregated facility-level TB notification data	• All patients with RR-TB who were notified and started on treatment.
Gap 4	124 (95%CI: 100-151)	7.1	Step 4 estimated cases minus Step 5 estimated cases	
Step 5. Successfully treated for TB	385 (95%CI: 358-409)	22.1	Add the facility-level short-course RR-TB treatment outcomes data (number successfully treated) adjusted for proportion of patients who were not evaluated to the number of RR TB who completed a traditional, long-course regimen* *Proportion of RR TB cases notified that were successfully treated using a long-course regimen extrapolated from 2017 estimates.	• Number of RR TB cases notified in 2018 that were started on a short-course regimen: 322 • Proportion of RR TB patients receiving a short-course regimen who were evaluated and completed treatment in 2018: 75.7% (95%CI: 70.6-80.4) • Number of RR TB cases notified in 2018 that were started on a long-course regimen: 187 • Proportion cured and completed treatment in 2017: 75.4% (95% CI: 69.8-80.4)

[1] Estimate derived from: Kapata N, Mbulo G, Cobelens F, et al. The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health*. 2015;20(11):1492-1500. This is the most recent Zambia national drug resistance survey. A higher estimate utilizing MDR-TB Plus chosen because it more closely coincides with current WHO estimates.

Table 3b. Estimation method for determining number of patients with RR TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall, No
Number of laboratory-confirmed RR-cases	-	-	627
Proportion of RR-TB patients notified in 2018, by HIV-status.[1]	59.1% (95CI: 54.6-63.6)	40.9% (95%CI: 36.4-45.4)	-
Number of RR-TB patients diagnosed in 2018, by HIV-status	627 x 59.1% (95CI: 54.6-63.6) = 371 (95%CI: 342-399)	627 x 40.9% (95%CI: 36.4-45.4) = 256 (95%CI: 228-285)	627
Number of RR-cases detected by Xpert	-	-	372
Number of RR-cases detected by Xpert, by HIV-status	372 x 59.1% (95CI: 54.6-63.6) = 220 (95%CI: 203-237)	372 x 40.9% (95%CI: 36.4-45.4) = 152 (95%CI: 135-169)	372
Combined sensitivity of Xpert for Rif-Resistance, by HIV status[2]	• Sensitivity of Xpert for TB: 81% (95%CI: 75% to 86%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RR-TB: 77.8% (95%CI 70.5-83.4)	• Sensitivity of Xpert for TB: 88% (95%CI: 83% to 92%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RIF-resist TB: 84.5% (95%CI 78.0-89.2)	-
RR-cases missed by Xpert	220 (95%CI: 203-237)/ .778 (95%CI .705-.834) – 220 = 63 (95%CI: 24-116)	152 (95%CI: 135-169)/ .845 (95%CI .780-.892) – 152 = 28 (95%CI: 0-64)	91 (95%CI: 23-180)
Number of RR-cases detected by MDR-TB plus	-	-	135
Number of RR-cases detected by MDR-TB plus, by HIV-status	135 x 59.1% (95CI: 54.6-63.6) = 80 (95%CI: 74-86)	135 x 40.9% (95%CI: 36.4-45.4 = 55 (95%CI: 49-61)	135
Combined sensitivity of MDR-TB plus*[3]	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 48.5% (95%CI: 40.1-55.9)	• Sensitivity of smear for TB: 76% (95%CI: 70-80) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 73.6% (95%CI: 66.9-78.4)	-
RR-cases missed by MDR-TB plus	80 (95%CI: 74-86) /.485 (95%CI: .401-.559) - 80 = 85 (95%CI: 52-134)	55 (95%CI: 49-61) / .736 (95%CI: .669-.784) - 55 = 20 (95%CI: 7-36)	105 (95%CI: 59-171)

Number of RR-cases detected by liquid culture (MGIT 960)*[4]			120
Number of RR-cases detected by liquid culture (MGIT 960)*[4], by HIV-status	120 x 59.1% (95CI: 54.6-63.6) = 71 (95%CI: 66-76)	120 x 40.9% (95%CI: 36.4-45.4 = 49 (95%CI: 44-54)	120
Combined sensitivity of liquid culture	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 49.6% (40.3-57.0)	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 75.4 (95%CI: 67.1-80.0)	-
RR-cases missed by liquid culture	71 (95%CI: 66-76) / .496 (95%CI: .403-.570) – 71 = 72 (95%CI: 61-83)	43 (95%CI: 49-54) / .754 (95%CI: .671-.800) – 43 = 16 (95%CI: 6-32)	88 (95%CI: 67-115)
Total microbiologically-missed cases	63 (95%CI: 24-116) + 85 (95%CI: 52-134) + 72 (95%CI: 61-83) = 220 (95%CI: 137-333)	28 (95%CI: 0-64) + 20 (95%CI: 7-36) + 16 (95%CI: 6-32) = 64 (95%CI: 13-133)	283 (95%CI: 149-466)
Received empiric therapy*	0	0	0
Total Missed cases	220 (95%CI: 137-333)	64 (95%CI: 13-133)	283 (95%CI: 149-466)

[1]Exact value from national TB laboratory register. [2]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593. [3]Estimated derived from: WHO. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Geneva: WHO; 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1, [4]Estimated derived from: Tortoli E, Benedetti M, Fontanelli A, Simonetti MT. Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Microbiol*. 2002;40(2):607-610.

Table 4. Drug-susceptible TB Care Cascade among HIV-positive individuals in Zambia in 2018

Variable	Cases, range	Proportion (%), range	Estimation method	Calculation
Step 1. Overall TB burden	43,411 (23,911-65,911)	100	WHO 2019 analysis of TB incidence in 2017 plus 50% of the number of undetected cases from 2018.	• TB incidence, 2018 (all): 36,000 (range, 23,000-51,000) • TB incidence, 2017 (all): 36,000 (range, 23,000-51,000) • Case detection rate, 2017: 58.8% (range, 41.5-92.1) • Estimated undetected cases 2017: 14,822 (range, 1,822-29,822) • 50% of undetected cases who have not died/self-cured: 7,411 (range, 911-14,911)
Gap 1	18,597 (0-40,495)	43.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	24,746 (95%CI: 24,290-25,349)	57.0	Add the number of missed cases to the total number of DS TB cases diagnosed (step 3).	• Number diagnosed: 23,133 (95CI: 23,106-23,154) • Number missed (table 2b): 1,613 (95%CI: 1,185-2,194)
Gap 2	1,613 (95%CI: 1,185-2,194)	3.7	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	23,133 (95%CI: 23,106-23,154)	53.3	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy (PTLTFU) [table 2c]; [assumed to be the same independent of HIV-status].	• PTLTFU estimate: 9.2% (95%CI: 9.1-9.3) • Number of HIV-positive patients notified in 2018: 21,012 (95%CI: 20,962-21,064)
Gap 3	2,121 (95%CI: 2,094-2,142)	4.9	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	21,012 (95%CI: 20,962-21,064)	48.4	Aggregated facility-level TB notification data adjusted for proportion of patients without an HIV test.	• DS TB: 19,332 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)
Gap 4	2,433 (95%CI: 2,337-2,529)	5.6	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	18,579 (95%CI: 18,535-18,625)	42.8	Aggregated facility-level TB treatment outcomes data (number successfully treated) adjusted for proportion of patients without an HIV test.	• DS TB: 17,624 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

Table 5. Drug-susceptible TB Care Cascade among HIV-negative individuals in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	27,344 (16,098-41,570)	100	Total number of DS TB cases minus number of DS TB cases among HIV-positive individuals	• Number of DS TB cases: 70,755 (range, 40,009-107,481) • Number of HIV-positive DS TB cases: 43,411 (23,911-65,911)
Gap 1	10,939 (98-24,620)	35.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	17,731 (95%CI: 17,324-18,276)	64.8	Total number of DS TB cases who accesses TB tests minus the number of DS TB cases who accessed TB tests among HIV-positive individuals	• Number of DS TB cases that accessed tests: 42,477 (95%CI: 41,614-43,625) • Number of HIV-positive DS TB cases diagnosed: 24,746 (95%CI: 24,290-25,349)
Gap 2	1,315 (95%CI: 927-1,846)	4.8	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	16,415 (95%CI: 16,395-16,431)	60.0	Total number of DS TB cases diagnosed minus the number of DS TB cases diagnosed among HIV-positive individuals	• Number of DS TB cases diagnosed: 39,549 (95%CI: 39,501-39,585) • Number of HIV-positive DS TB cases diagnosed: 23,133 (95%CI: 23,106-23,154)
Gap 3	1,505 (95%CI: 1,486-1,520)	5.5	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	14,910 (95%CI: 14,858-14,960)	54.5	Total number of DS TB cases notified minus the number of DS TB cases among HIV-positive individuals notified	• Number of DS TB cases notified: 35,922 • Number of HIV-positive DS TB cases notified: 21,012 (95%CI: 20,962-21,064)
Gap 4	1,185 (95%CI: 1,089-1,281)	4.3	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	13,725 (95%CI: 13,679-13,769)	50.2	Total number of DS TB cases successfully treated minus the number of DS TB cases among HIV-positive individuals successfully treated	• Number of DS TB cases treated: 32,304 • Number of HIV-positive DS TB cases treated: 18,633 (95%CI: 18,535-18,725)

BMJ Open

The tuberculosis care cascade in Zambia: identifying the gaps in order to improve outcomes

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044867.R1
Article Type:	Original research
Date Submitted by the Author:	10-Mar-2021
Complete List of Authors:	Lungu, Patrick; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia; University of Zambia University Teaching Hospital, Department of Internal Medicine Kerkhoff, Andrew; University of California San Francisco, ; San Francisco General Hospital and Trauma Center, Kasapo, Clara; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Mzyece, Judith; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Nyimbili, Sulani; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Chimzizi, Rhehab; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Silumesi, Andrew; Ministry of health Zambia Kagujje, Mary; Center for Infectious Disease Research in Zambia Subbaraman, Ramnath; Tufts University School of Medicine, Department of Public Health and Community Medicine Muyoyeta, Monde ; Center for Infectious Disease Research in Zambia Malama, Kennedy; The Zambian Ministry of Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Global health, Health services research
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The tuberculosis care cascade in Zambia: identifying the gaps in order to improve outcomes

Short title: TB Care Cascade in Zambia

AUTHORS: Patrick Lungu[1,2*], Andrew D. Kerkhoff[3*], Clara C. Kasapo[1], Judith Mzyece[1], Sulani Nyimbili[1], Rhehab Chimzizi[1], Andrew Silumesi[4], Mary Kagujje[5], Ramnath Subbaraman[6], Monde Muyoyeta[5], Kennedy Malama[4]

Affiliations:

[1]National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia
[2]Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia
[3]Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco, San Francisco, CA, USA
[4]Ministry of Health, Lusaka, Zambia
[5]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia
[6]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

*PL and ADK contributed equally.

Corresponding author:
Dr. Andrew Kerkhoff, MD, PhD
Email: Andrew.Kerkhoff@ucsf.edu

Article type: Original article

Keywords: Tuberculosis, care cascade, loss to follow-up, Zambia, HIV, rifampicin resistance

Abstract

Objectives: Tuberculosis (TB) remains a leading cause of morbidity and mortality in Zambia, especially for people living with HIV (PLHIV). We undertook a care cascade analysis to quantify gaps in care and align program improvement measures with areas of need.

Design: Retrospective population-based study.

Setting: We derived national-level estimates for each step of the TB care cascade in Zambia. Estimates were informed by WHO incidence estimates, nationally aggregated laboratory and notification registers, and individual-level program data from four provinces.

Participants: All individuals with active TB disease in Zambia in 2018. We characterized the overall TB cascade as well as disaggregated by drug-susceptibility results and HIV status.

Results: In 2018, the total burden of TB in Zambia was estimated to be 72,495 (range, 40,495-111,495) cases. Of these, 43,387 (59.8%) accessed TB testing, 40,176 (55.4%) were diagnosed with TB, 36,431 (50.3%) were started on treatment and 32,700 (45.1%) completed treatment. Among those who did not complete the care cascade, 73.1% were lost prior to accessing diagnostic services, 8.1% prior to diagnosis, 9.4% prior to initiating treatment and 9.4% prior to treatment completion. PLHIV were less likely than HIV-negative individuals to successfully complete the care cascade (42.8% vs. 50.2%;p<0.001). Among those with rifampicin-resistant TB, there was substantial attrition at each step of the cascade and only 22.8% were estimated to have successfully completed treatment.

Conclusions: Losses throughout the care cascade resulted in a large proportion of individuals with TB not successfully completing treatment. Ongoing health systems strengthening and patient-centered engagement strategies are needed at every step of the care cascade; however, scale-up of active case finding strategies is particularly critical to ensure individuals with TB in the population reach initial stages of care. Additionally, a renewed focus on PLHIV and individuals with drug-resistant TB is urgently needed to improve TB-related outcomes in Zambia.

Strengths and limitations of this study

- The national tuberculosis (TB) care cascade for Zambia in 2018 was characterized in order to identify gaps in care.
- The TB care cascade was constructed for all TB patients as well as according to drug-susceptibility result and HIV status.
- The analysis was informed by a published set of methodologies and utilized several data sources to derive estimates.
- Enhanced TB surveillance programs, including the use of unique TB patient identifiers, would allow for real-time monitoring and improved estimates to inform programmatic strengthening.

Background

The WHO End TB strategy aims to reduce tuberculosis (TB) incidence by 90% and TB-related deaths by 95% between 2015 and 2035 [1]. While many high burden countries in sub-Saharan Africa, including Zambia, have demonstrated large reductions in new TB cases and associated mortality, there remains significant need for improved TB care delivery [2]. TB remains a leading cause of morbidity and mortality in Zambia, especially among people living with HIV (PLHIV) [3,4]. In 2019, there were approximately 59,000 new individuals with active TB disease in Zambia (incidence rate 333 individuals with TB per 100,000 people) that resulted in 15,400 TB-related deaths, of which 62% were among PLHIV [4].

The HIV "cascade of care" is a public health model that outlines the key engagement steps required for PLHIV to ultimately achieve an undetectable viral load. This model has been widely applied by HIV programs globally to inform and strengthen HIV care and delivery and ultimately, significantly increase the number of PLHIV who know their HIV status, are started on ART and have suppressed viral loads [5]. Similarly, a national TB care cascade can provide key insights to identify and quantify gaps in the diagnosis and care of TB patients that could then help guide programmatic and research priorities by aligning limited resources with the areas of greatest need [6,7]. However, to-date, only three high burden TB countries - South Africa, India, and Madagascar - have undertaken and published national-level TB care cascade analyses [8–10].

We sought to construct a national TB cascade of care for Zambia to evaluate care delivery for individuals with active TB disease through enumeration of gaps in the overall care cascade in 2018 as well as disaggregated by rifampicin susceptibility results and HIV status. Estimates were derived using multiple data sources and the overall approach was informed by a recently published methodology for constructing TB care cascades [7].

Methods

Setting

Zambia has an estimated population of 18,400,000 people [11]. It has a high prevalence of HIV (11.5% among adults aged 15-49 years old), and it is estimated that at least 1.2 million persons

are living with HIV [12]. TB is a major public health problem in Zambia [3]; during the last national TB prevalence survey conducted in 2013 and 2014, the prevalence of microbiologically-confirmed TB was estimated to be 638 per 100,000 persons and was five-times higher among HIV-positive individuals compared to HIV-negative individuals [13].

Testing and treatment for TB is almost universally provided within Zambia's public health system. While exact estimates are not available, likely <1% of all individuals with TB are detected and managed within Zambia's private sector and the large majority are reported to Zambia's National TB Program (NTP) – this assumption is informed by a national data quality audit conducted in 2019 (unpublished). Within the public health sector, the direct costs of all TB diagnostics and treatment are provided free of charge. In 2018, Xpert MTB/RIF was the recommended first-line diagnostic for all individuals undergoing evaluation for possible TB (pulmonary or extra-pulmonary) in Zambia as well as initial drug-susceptibility testing (DST) [14]; however, it was not universally available at all facilities, in which case routine TB investigations included acid fast bacilli (AFB) fluorescence or Ziehl-Neelsen microscopy and chest radiography, where available. Among those with confirmed rifampicin-resistant (RR) or multidrug-resistant (MDR) TB, it was recommended that either liquid culture or a molecular line probe assay should be used as follow-on tests for further DST [14]. First line TB treatment was provided to all patients without evidence of rifampicin-resistance and consisted of isoniazid, rifampicin, ethambutol and pyrazinamide for 6-9 months in conformity with WHO recommendations [15]. In 2018, Zambia began scaling up shorter treatment regimens comprised of new and repurposed TB drugs for 9-12 months for eligible RR- and MDR-TB patients – this accounted for the majority of patients [16,17]; however, some patients still received longer MDR-TB treatment regimens comprised of several TB drugs, including an injectable agent, for at least 20 months.

In Zambia, all patients diagnosed with TB are notified in a paper-based register and initiated on TB therapy at the corresponding TB treatment facility, which is also responsible for documentation of the treatment outcome of the patient. Data on diagnostic outcomes (laboratory register), notifications and treatment outcomes (notification register) are aggregated from each facility through the district office to the provincial level and then the national level on a monthly basis.

Ethics

Because this was a retrospective, population-level analysis without the use of any patient identifiers, the University of Zambia Biomedical Research Ethics Committee determined that this study met the criteria for exempt-status.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this analysis. However, there are plans to disseminate the findings to TB communities through TB stakeholder meetings with neighborhood health committees, which includes former TB patients and other community TB advocates.

TB Cascade Data Sources

Several data sources were used to inform estimates within each of the five steps of the care cascade (**Table 1, Supplementary Appendix**). To inform estimates of the overall burden of TB in Zambia in 2018 (Step 1), WHO estimates of TB incidence from 2018 and 2017 were utilized [2,18–20]**.** The proportion of total individuals with TB estimated to be rifampicin-resistant was derived using estimates from the most recent national survey of TB drug resistance in Zambia [21]; this source was chosen in order to ground estimates of RR-TB in empiric data, however, higher-end estimates from the latest Zambian national survey of TB drug resistance in 2008 were used to more closely align with WHO incidence estimates for RR-TB in 2018. Diagnostic outcomes (Steps 2 and 3) were informed by a nationally aggregated database of TB diagnostics from 2018, which includes the number and type of investigations (Xpert or smear microscopy) and the number of TB patients detected according to type of TB investigation and HIV status. All treatment outcomes (Steps 4 and 5) were informed by a nationally aggregated TB treatment register from 2018.

Individual level programmatic data from four Zambian Provinces (Eastern, Lusaka, Southern, Western) regarding all patients investigated for TB and those started on treatment between January 1st and December 31st 2017 (n=43,896, n=11,814, respectively) was used to determine: (a) the proportion of patients who had both positive Xpert and smear microscopy results as well as (b) the proportion of patients who were Xpert or smear-negative, but received empirical TB

therapy. This helped to further refine estimates for Steps 2 and 3 by accounting for and removing duplicate patients (**Supplementary Appendix**). Patient-level data was only available from 4 out of 10 provinces; however, they account for nearly 60% of Zambia's national TB notifications and the range of socioeconomic characteristics of individuals as well as their access to healthcare services are representative of the other 6 provinces [22,23]. Unfortunately, robust data from 2018 to inform these estimates were unavailable – thus, we utilized 2017 data because it was well-characterized and temporally close to the year for which we sought to characterize the TB care cascade.

Diagnostic sensitivity estimates of Xpert [24] and smear microscopy [25,26] for the detection of TB stratified according to HIV status, as well as Xpert [24], molecular line probe assays [27] and liquid culture [28] for rifampicin-resistance were informed by previously published systematic reviews and meta-analyses.

TB Cascade Estimation Methods

We calculated national-level estimates for each step of the TB care cascade in Zambia in 2018 (**Table 1, Supplementary Appendix**). This included: Step 1: The total burden of active TB disease (individuals with prevalent TB in 2018); Step 2: the total number of individuals with TB who accessed TB testing; Step 3: the total number who were diagnosed with TB; Step 4: the total number who were notified and started on TB treatment; Step 5: the total number who successfully completed TB treatment. Each step of the cascade as well as the overall TB care cascade was calculated among: all patients and disaggregated according to rifampicin-resistance result (RR-TB and drug-susceptible TB [DS-TB]) and, among those with drug-susceptible (DS) TB, by HIV status. Rifampicin resistant TB was defined as the detection of rifampicin resistance on any clinical specimen using Xpert, molecular line probe assay or liquid culture; this definition therefore encompassed all patients with MDR-TB and extensively drug resistant TB (XDR-TB). DS-TB was defined as any TB case without known rifampicin resistance; thus, there is a possibility that patients with other forms of drug-resistance, including isoniazid monoresistance may have been included in this definition. However, unless rifampicin resistance is detected, TB drug susceptibility testing is not routinely performed in Zambia – this reflects the clinical reality of many high burden TB settings and conforms with WHO recommendations

The approach to all estimates followed recommendations outlined in a published set of methods for constructing national-level TB care cascades [7]. An overview of the approach used to calculate each step of the TB care cascade is summarized in **Table 1** and is described in brief below; however, a highly detailed summary of all assumptions, calculations, estimates, and data sources is summarized in the **Supplementary Appendix**.

We first started with Step 4 (the total number of patients who were notified and started on TB treatment - including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated individuals [29]) and Step 5 (the total number who successfully completed TB treatment), which were both directly informed by exact values from aggregated facility-level notification data. Step 3 (the total number who were diagnosed with TB) was then back calculated from the number of individuals notified (Step 4) and the proportion of patients who were estimated to have been lost-to-follow-up prior to initiation of TB therapy (pre-treatment loss-to-follow-up [PTLTFU]), which was informed by aggregated facility-level laboratory data. Step 2 (the total number of individuals with TB who accessed TB testing) was calculated by adding the number of individuals with TB who would not have been microbiologically diagnosed due to the incomplete sensitivity of TB diagnostic tests (based upon published reports), corrected for the number of test-negative TB patients who were empirically diagnosed, to the number of total TB patients diagnosed (Step 3). The overall approach for Steps 2-5 was similar for both DS-TB and RR-TB (**Table 1 and Supplementary Appendix**). The overall TB burden (all forms) was estimated using the WHO TB incidence estimate for 2018, plus 50% of the number all individuals with TB that remained undiagnosed in 2017; a 50% estimate has previously been utilized and assumed that the remaining 50% of undiagnosed individuals with TB in 2017 either self-cured or died [9,30]. To determine the total number of individuals with rifampicin resistant TB (Step 1), we multiplied the overall TB burden by the proportion of all patients who had rifampicin resistance detected during the Zambian national drug resistance survey [21]. The total number of individuals with DS-TB was calculated using the total TB burden minus the number of RR-TB cases.

All "gaps" between each step were calculated by taking the difference in the total number of individuals with TB and the uncertainty estimate (either 95% confidence intervals or range) between the succeeding and proceeding step. All TB care cascades were depicted graphically using bar charts representing the absolute number of cases and associated uncertainty measurement (if applicable). For each step of each cascade, proportions relative the total TB burden (Step 1) as well as relative to the prior step were calculated. It should be noted that several steps of the cascade utilized exact numbers from aggregated facility-level programmatic data (steps 3, 4, and 5); for the purposes of these analyses, data were assumed to be accurate and complete; however, such data may be incompletely recorded and a small proportion may be entered incorrectly - estimates of uncertainty around exact values from programmatic data were unavailable. Furthermore, unique patient identifiers are not available within Zambia's NTP and thus this analysis does not present a cohort of individuals that were tracked through each step of the TB care cascade; while we assumed for the purposes of this analysis that the same patients were being characterized at each step of the cascade, one cannot exclude the possibility that different individuals are being captured at different steps of the care cascade.

Evaluating Diagnostic and Treatment Outcomes

To understand any progress that may have underpinned the 2018 TB care cascade, we also evaluated TB diagnostic and treatment completion trends from 2015 to 2018. Using facility-level aggregated laboratory data, we plotted (a) the total number of sputum Xpert tests undertaken each year against the total number of pulmonary TB cases diagnosed each year, including the proportion that was microbiologically confirmed as well as (b) the total number of Xpert tests undertaken (on any specimen) each year against the total number of RR-TB cases diagnosed and notified each year. We also plotted the proportion (and corresponding 95% confidence interval) of TB patients each year who started TB treatment that successfully completed it, disaggregated according to TB type: (1) new/relapse pulmonary TB – overall (2) HIV-positive new/relapse pulmonary TB, (3) HIV-negative new/relapse pulmonary TB, (4) retreatment TB not including individuals who experienced relapse, and (5) extra-pulmonary TB.

Results

Overall National TB Care Cascade for 2018

In 2018, the overall burden of TB in Zambia was estimated to comprise 72,495 individuals with TB (range: 40,495-111,495; **Table 2; Figure 1a**). Of the total burden of individuals with TB, 43,387 (range, 42,390-44,710; 59.8%) were estimated to have sought care for their TB illness and undergone microbiologic TB testing. Among these individuals 40,176 (range, 40,128-40,212; proportion of total TB burden - 55.4%) were diagnosed with TB, 36,431 (exact value; proportion of total TB burden – 50.3%) were notified and initiated on TB therapy and 32,700 (exact value; proportion of total TB burden – 45.1%) completed TB therapy. Therefore, 39,795 (range, 8,191-79,191; 54.9%) of the estimated individuals with TB in 2018 did not complete the care cascade (**Table 3**). Individuals who did not seek care for their TB illness or who sought care but did not undergo microbiological TB testing accounted for 29,108 (range, 0-66,777; 73.1%) individuals with TB lost along the cascade in 2018 (**Table 3)**; suboptimal empirical diagnosis of individuals with TB who had negative microbiological test results (due to incomplete diagnostic sensitivity of these tests) contributed to an additional 3,211 (95%CI, 2,262-4,506; 8.1%) missed TB cases, losses-to-follow-up prior to TB treatment initiation accounted for 3,745 (95%CI, 3,697-3,781; 9.4%) patients lost, and unfavorable outcomes (loss to follow-up, death, and treatment failure) prior to TB treatment completion accounted for 3,731 (exact value; 9.4%) patients lost.

TB Care Cascade by Drug Susceptibility Result

We estimated the burden of individuals with DS-TB in 2018 to be 70,755 (range, 40,009-107,481) - approximately 97.6% of the total TB burden. The DS-TB cascade was largely similar to the overall TB cascade with 32,304 (exact value; 45.7%) of all individuals being diagnosed with TB, initiating on and completing TB treatment (**Table 2; Figure 1b)**. The total number of rifampicin-resistant (RR) TB cases was estimated to be 1,740 (range, 486-4,014), or 2.4% of the total TB burden. Compared to individuals with DS-TB, individuals with RR-TB were substantially less likely to access microbiological TB testing (52.3% vs. 60.0%, p<0.001), have their TB diagnosed (68.9% vs. 93.1%, p<0.001), be notified and initiated on TB treatment (81.2% vs. 90.8%, p<0.001) and to complete TB therapy (77.8% vs. 89.9%, p<0.001) (**Figure 1c)**. Thus, only 396 (exact value; 22.1%) individuals with RR-TB completed the TB care cascade. The

majority of those with RR-TB along the pathways were due to individuals who did not seek care or who did not have access to TB and/or drug susceptibility testing – accounting for 830 cases (range, 0-2,961; 61.7%, **Table 3**); however, 283 (95%CI, 149-466; 21.1%) of lost RR-TB cases were among those who accessed TB testing and had RR-TB missed, 118 (exact value; 8.8%) were among those who had RR-TB detected but were not notified and started on appropriate TB therapy, and 113 (exact value; 8.4%) were among those who did not complete RR-TB therapy (**Table 3**).

Drug Susceptible TB Care Cascade by HIV status

Of 70,755 individuals with drug-susceptible TB in 2018, 43,411 (range, 23,911-65,911; 61.4%) were estimated to be among people living with HIV. Compared to patients with DS-TB who were HIV-negative, HIV-positive patients with DS-TB were less likely to access microbiological TB testing (57.0 vs. 64.8%, p<0.001) and were less likely to complete TB treatment (88.4% vs. 92.1%, p<0.001). This resulted in a lower overall proportion of HIV-positive patients compared to HIV-negative patients completing the TB care cascade (42.8% vs. 50.2%, p<0.001; **Table 2; Figures 1d and 1e**). For both HIV-positive and HIV-negative patients with DS-TB, the largest loss in the care cascade was due to patients not accessing microbiological TB testing resulting in 18,597 (range, 0-40,495; 75.2%) and 10,939 (range, 98-24,620; 70.6%) missed patients, respectively.

TB Diagnosis Trends from 2015 to 2018

Between 2015 and 2018 Xpert MTB/RIF was increasingly utilized as the first-line TB diagnostic tool in Zambia where 24,140 Xpert tests were sent for suspected pulmonary TB in 2015, which increased to 163,470 sent in 2018 (**Figure 2a**). During this same period, the number of sputum AFB smear microscopy investigations decreased from 95,300 in 2015 to 25,323 in 2018. While there was a small decrease in the absolute number of pulmonary TB cases diagnosed and notified in 2018 compared to 2015 (31,272 vs. 33,452), the proportion of microbiologically-confirmed TB cases that were notified during that period, substantially increased (56.0% [95CI, 55.5-56.6] vs. 44.1% [95%CI, 43.6-44.7]; **Figure 2a**). The scale-up of Xpert testing between 2015 and 2018 was also associated with a more than three-fold increase in the annual number of RR cases detected (627 vs. 196), and more than five-fold increase in the annual number of

rifampicin resistant TB cases that were notified and started on appropriate TB treatment (509 vs. 99; **Figure 2b**). During this period, there was corresponding reduction in the proportion of PTLTFU RR-TB cases from 49.5% in 2015 to 18.8% in 2018 (p<0.001).

TB Treatment Completion Trends from 2015 to 2018

Finally, we examined trends in the proportion of DS-TB patients who completed TB treatment once they were notified and initiated on therapy (**Figure 3**). Among new/relapse pulmonary TB cases, treatment completion rates steadily increased between 2015 and 2018 (86.2 vs. 90.3%, p<0.001). There was also a trend towards improved TB treatment completion rates from 2015 to 2018 among retreatment pulmonary TB cases (84.4% vs. 87.2%, p=0.06), however completion rates declined from 2017 to 2018 (95.0% vs. 87.2%, p<0.001). From 2015 to 2018, the proportion of patients with extrapulmonary TB completing TB treatment also improved (80.6% vs. 87.8%, p<0.001). The proportion of HIV-positive patients completing TB therapy remained relatively unchanged from 2015 to 2018 (87.3% vs. 88.4%, p=0.001). Improvements in treatment completion rates from 2015 to 2018 were seen among patients who had a negative or unknown HIV status (82.4% vs. 91.8%, p<0.001) although, there was a small decline between 2017 and 2018 (93.7 vs. 91.8%, p<0.001; **Figure 3**). In 2018, a lower proportion of HIV-positive TB patients completed therapy compared to HIV-negative patients (difference 3.4%, p<0.001). Differences in the proportion of patients completing TB therapy according to HIV status were driven by a higher absolute number and proportion of cases that died or were lost-to-follow-up during treatment among HIV-positive individuals compared to HIV-negative individuals (**Supplementary Table 1).**

Discussion

In this study we found that less than half of all TB cases in Zambia in 2018 were diagnosed with TB, initiated on TB treatment and completed therapy. We identified important losses at each step of the TB care cascade, however, we estimate that more than 40% of all individuals with TB in Zambia are not accessing microbiological TB testing – this accounted for nearly three-quarters of the estimated number of cases lost throughout the cascade. These results highlight important research and programmatic priorities for improving TB care and TB-related outcomes in Zambia.

This represents the fourth national TB care cascade that has been characterized from a high burden TB country and builds upon similar analyses from South Africa, India, and Madagascar [8–10]. Our overall TB care cascade results are similar to those from these countries that each found that only about 50% of all TB patients were progressing through all steps of the care cascade and completing TB treatment. In India the largest losses in the care cascade were among those who did not access TB testing (28% of all cases) [8], in Madagascar the largest losses in the cascade were among those who were not diagnosed with TB despite seeking care and accessing a TB diagnostic facility (26% of all cases) [10], while in South Africa steady losses were seen prior to TB diagnosis (12% of all cases), prior to starting TB treatment (13% of all cases) and prior to successful completion of TB therapy (17% of all cases) [9]. In Zambia, 40% were estimated to have not accessed TB testing, while 4-5% of all TB cases were lost at each subsequent step of the care cascade. These differences highlight specific programmatic needs at different steps within the TB care cascade for each country and provides insight into the unique challenges that they each face.

Our results are consistent with several TB prevalence surveys suggesting that a large proportion of individuals with TB face barriers to healthcare seeking, barriers to accessing microbiological TB testing, or both [31,32]. Unfortunately, we are not able to discern whether the estimated 40% gap in patients not accessing TB microbiological investigations is predominantly driven by (a) individuals who fundamentally lacked access to primary health and TB facilities, (b) individuals who either delayed or never presented to TB testing facilities for evaluation of their illness, or (c) individuals who sought care at health facilities, but their illness was not suspected to be TB and thus they never had TB testing undertaken [33]. After onset of symptoms, individuals with undiagnosed TB may have long and complex journeys to TB care as they often face many barriers to care-seeking and accessing TB services (e.g., lack of knowledge, lack of social support, lack of time/finances, TB/HIV-related stigma, cultural and gender norms) [32,34,35]. In the last Zambian national TB prevalence survey conducted in 2013 and 2014, only 60% of previously undiagnosed individuals with TB were symptomatic, of whom 50% had sought care for their illness at a health facility [13]. Furthermore, once patients do access healthcare services,

their TB illness may be missed – this has been shown to be a common problem in recent standardized patient studies conducted in Kenya [36], India [37] , and China [38].

Collectively, this suggests that both community-based and facility-based active TB case finding strategies, as well as training of healthcare providers to improve recognition of and testing for TB, are likely to be important to activities to increase detection of individuals with TB in Zambia Community-based active TB case finding may help overcome individuals' barriers to health-seeking and accessing TB services, possibly resulting in a greater absolute number of TB patients diagnosed and patients who are detected earlier [39–41]. However, effective and sustainable community-based active TB case finding strategies are not well-described and represent an urgent TB research need [32,42]. There is strong evidence demonstrating that facility-based, active TB case finding strategies are efficient and may yield a large number of cases that would otherwise have been missed, especially in high burden settings [43–46]. A recent study evaluating a multicomponent active TB case finding strategy in a high burden primary health care facility in Lusaka, Zambia found that total TB notifications increased by 35% during the intervention period; of the total TB cases, 91.5% were from facility-based case finding interventions while 8.5% were from community-based case finding interventions [46]. One important component of this strategy was the implementation of patient-friendly TB fast-track points at health facilities that improved access by allowing individuals with TB symptoms to skip the regular que and undergo rapid screening and testing for TB. Further research is needed to understand what potential strategies to improve TB care engagement and diagnosis are most preferred by and acceptable to community members in high-burden settings.

We estimate that nearly 10% of individuals diagnosed with TB were lost from follow-up prior to initiation of TB treatment (PTLTFU). PTLTFU is common in many high-burden settings as demonstrated by a systematic review that found that 4-38% (weighted proportion 18%) of TB patients in sub-Saharan Africa were lost at this step in the cascade [47]. This may be accounted for by patients who died prior to initiation of therapy – a common finding among such patients – and patients who cannot be traced after diagnosis either due to missing/incorrect contact information, or because they have moved away. A recent qualitative study among TB patients and health care workers (HCW) in India provided further understanding of factors that may

contributed to PTLTFU [48]. The authors identified challenges and constraints related to organizational and administrative barriers resulting in patient disengagement from TB services over frustration as well as negative HCW attitudes and behaviors resulting in patient distrust and feeling that their autonomy had been violated. There is an important need to design, evaluate and implement strategies that may address patient-level and health system factors and reduce PTLTFU [47]. It should be noted that pre-treatment loss-to-follow-up estimates may be overestimated because they fail to account for individuals who were in fact started on TB therapy, but were not officially registered and therefore never notified to the NTP (under-notification). Zambia's NTP has recently completed a study to estimate the proportion of patients who are diagnosed but not notified as well as the proportion of those who are started on treatment but never reported. This study will yield improved estimates of pre-treatment loss-to-follow-up, which will allow for improved evaluations of programmatic changes that aim to improve TB diagnosis and linkage to TB treatment and care.

We found that important progress has been made in Zambia with regard to microbiological TB diagnosis and TB treatment completion from 2015 to 2018. During this period there was a massive effort to scale-up the availability of Xpert MTB/RIF as the first-line TB diagnostic for all forms of TB. This was associated with a 12% increase in the proportion of TB patients who were microbiologically-confirmed (2,692 additional annual drug-susceptibility patients). Importantly, because Xpert also provides rapid simultaneous detection of rifampicin-resistance, its scale-up was also associated with a three-fold increase in RR-TB patients detected and a five-fold increase in the number of RR-TB patients who were notified and started on TB treatment. Zambia is currently preparing to scale-up Xpert Ultra cartridges, which when paired with continued efforts to decentralize Xpert testing, should allow for further gains in the detection of HIV-associated TB, extra-pulmonary TB, and RR-TB [49]. There was also evidence of improved TB treatment completion rates for nearly all forms of TB between 2015 and 2018. While it is important to recognize progress that has been made, smaller but critically important gaps in the TB care cascade remain due to missed diagnoses and lack of treatment completion. Further efforts to expand access to microbiological TB testing and interventions to bolster TB treatment adherence that are grounded in person-centered care approaches - such as decentralization of

services coupled with improved education and communication as well as material and psychological support - are needed [50,51].

PLHIV accounted for more than 60% of TB cases in Zambia and were more likely to be lost at several steps of the cascade compared to HIV-negative individuals. This finding emphasizes the need to strengthen HIV-TB collaborative activities [32,52]. Due to non-specific clinical presentations and radiographic findings, one of the most important challenges to improving HIV-associated TB outcomes remains TB diagnosis [53]. Non-specific symptoms may delay care-seeking among PLHIV, and without systematic TB screening among PLHIV presenting to and in-care, the diagnosis of many TB cases may be further delayed or missed. Systematic screening for TB at each clinical presentation [54] must be coupled with access to improved microbiological diagnostic tools such as Xpert Ultra [55] and urine LAM [55,56] testing to facilitate rapid TB detection and TB treatment initiation in order to minimize pre-treatment loss-to follow-up and improve clinical outcomes. Compared to HIV-negative patients, HIV-positive patients were less likely to complete TB therapy, and TB treatment completion rates among PLHIV did not significantly change over a four-year period from 2015 to 2018. Previously, a study among PLHIV in Zambia found that a large number of individuals LTFU from HIV services had died and that programmatic mortality rates were substantially under-reported [22]; this suggests that mortality among PLHIV LTFU from TB treatment services is high and that TB-related mortality among PLHIV in Zambia is likely underestimated. The implementation of tailored interventions to improve adherence to TB treatment [50,57] as well as antiretroviral therapy [58] among this highly vulnerable population therapy are needed.

Notably, we found that less than one quarter of rifampicin resistant TB cases in 2018 were detected, started on appropriate treatment and completed appropriate therapy. This was despite improved access to rapid drug susceptibility via the scale-up of Xpert MTB/RIF testing from 2015 to 2018 and shorter and simplified drug-resistant TB regimens being introduced in 2018 [16]. The high rate of attrition of rifampicin-resistant TB patients throughout the care cascade argues for the need for specific investments in systems strengthening to improve drug resistant TB diagnosis and treatment in Zambia, mirroring this dire need in most high TB burden countries [18,32,59,60]. One important contributing factor to the large number of RR-TB patients not

accessing DST is the high proportion of patients who are being diagnosed clinically and/or on the basis of radiological findings only – this accounted for approximately 44% of pulmonary TB cases in Zambia in 2018. Notably, the scale-up of Xpert testing between 2015 to 2018 was associated with a more than 30% reduction in the proportion of RR-/MDR-TB cases that were lost-to-follow-up after diagnosis and prior to initiation of treatment – this is likely due to the substantially faster detection of rifampicin resistance compared to conventional culture-based methods. Collectively, this demonstrates the importance of continued efforts to expand access to Xpert testing in Zambia in order to facilitate confirmation of TB diagnoses coupled with rapid detection of rifampicin resistance. While the implementation of existing diagnostic tools as well as improved DR-TB treatment regimens must be optimized, there remains a continued need for the development of rapid low-cost drug susceptibility testing (DST) that can be scaled-up to provide decentralized access to first- and second-line DST aligned with current treatment recommendations [61], as well as continued progress towards shorter, less toxic, and more effective DR-TB treatment regimens [62].

This study utilized a validated analysis method [7] incorporating a number of data sources to derive nationally representative estimates of the TB care cascade in Zambia; however there were some limitations. As with other published TB cascades analyses, there is uncertainty around the estimates, especially the overall number of TB cases. The total burden of TB was calculated using indirect estimates from modelling that were based upon case notification data and a prior national TB prevalence survey. We derived a conservative estimate of the total TB burden that accounted for missed cases from the prior year [9] and that therefore may be a more appropriate estimate than measurements of TB incidence, which are rarely feasible to directly estimate [63]. Due to a lack of a unique national patient identifier, we were unable to link specific individuals with their outcomes as they progressed through the TB care cascade and thus unique individuals in one step of the cascade may differ from those in the following step; where possible, we attempted to account for duplicate diagnostic and treatment data, which was uncommon. Implementation of a unique TB patient identifier, and an improved TB data surveillance program with enhanced data integration would greatly improve future estimates and allow for real time individual-level, facility-level, and sub-national-level data to inform program strengthening.

Given the potential importance of gender to TB epidemiology [31,64] and potential differential health-seeking behaviors and access to TB services [35,65,66], we sought to characterize the TB care cascade among men and women. For example, the prevalence of TB among men in Zambia's first national TB prevalence survey in 2013/2014 was almost twice as high as that among women (833 vs. 487 cases per 100,000 persons) [13] and men with presumptive TB were less likely to have sought care for their symptoms than women (31.4% vs. 38.4%) [67]. Unfortunately, sex-disaggregated data sources were not available that would have allowed for each step of the cascade to be estimated. It is important that TB programs collect sex-disaggregated diagnostic and treatment data to help ensure equity in access and treatment benefits. Additionally, because core incidence, diagnosis, notification and treatment numbers are from 2018, we feel our analysis accurately represents the national TB care cascade in 2018; however, PTLTFU estimates were informed by patient-level data from 2017 and the proportion of cases with rifampicin resistance were informed by higher-end estimates from the most recent national drug resistance survey conducted in 2008 [21]. An updated drug resistance survey is currently underway and will provide new estimates that will better guide programmatic priorities. Finally, to our knowledge, there are no locally or regionally-representative estimates of TB relapse rates after documented TB treatment completion. This is an important quality metric of individuals' adherence to therapy as well as TB treatment programs and should be assessed in future research studies [7].

In conclusion, in 2018 only 45% of individuals with TB in Zambia completed the TB care cascade, and most losses were among patients who never accessed TB testing. Additionally, only 22% of all RR-TB patients successfully completed appropriate TB treatment and HIV-positive patients had substantially worse TB outcomes compared to HIV-negative patients. Our results suggest that continued systems-strengthening coupled with patient-centered engagement strategies are required throughout the TB cascade of care, however, implementation of active TB case finding strategies coupled with a renewed focus on those with rifampicin-resistance and PLHIV are urgently needed to improve TB-related outcomes and TB control in Zambia.

Contributions

PL, ADK and MM conceived the study. PL, RC, AS and KM were responsible for project administration. CCK, JM, and SN collected and organized the data. ADK conducted the analysis and developed the figures with input from PL, MM, RS, MK, CCK, JM, SN, RC, AS, and KM. ADK, PL, and MM wrote the first draft of the manuscript. All authors contributed to interpretation of data and editing of the article and approved the final version of the manuscript before submission.

Funding

ADK was supported by the National Institute of Allergy and Infectious Diseases (Grant No T32 AI060530).

Disclaimer

The funding sources had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the manuscript for publication.

Data availability statement

All data relevant to this study are included in the article or uploaded as supplementary information.

Competing Interests

All authors declare no competing interests.

References

1 WHO. The End TB Strategy. World Health Organization, Geneva; 2015. http://www.who.int/tb/End_TB_brochure.pdf?ua=1

2 WHO. World Health Organization. Global Tuberculosis Report 2018. World Health Organization, Geneva; 2019. https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf. 2019.

3 Centers for Disease Control. CDC in Zambia. Center for Disease Control and Prevention, Atlanta; 2017. Published Online First: 2017.https://www.cdc.gov/globalhealth/countries/zambia/pdf/Zambia_Factsheet.pdf

4 World Health Organization. Global Tuberculosis Report 2020. World Health Organization, Geneva; 2020.

5 Medland NA, McMahon JH, Chow EP, *et al.* The HIV care cascade: a systematic review of data sources, methodology and comparability. *J Int Aids Soc* 2015;**18**:20634. doi:10.7448/ias.18.1.20634

6 Reid MJA, Goosby E. Lessons learned from the HIV care cascade can help End TB. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2017;**21**:245–6. doi:10.5588/ijtld.17.0027

7 Subbaraman R, Nathavitharana RR, Mayer KH, *et al.* Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLoS Medicine* 2019;**16**:e1002754-18. doi:10.1371/journal.pmed.1002754

8 Subbaraman R, Nathavitharana RR, Satyanarayana S, *et al.* The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. *PLoS Medicine* 2016;**13**:e1002149-38. doi:10.1371/journal.pmed.1002149

9 Naidoo P, Theron G, Rangaka MX, *et al.* The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. 2017;**216**:S702–13. doi:10.1093/infdis/jix335

10 Knoblauch AM, Lapierre SG, Randriamanana D, *et al.* Multidrug-resistant tuberculosis surveillance and cascade of care in Madagascar: a five-year (2012–2017) retrospective study. *Bmc Med* 2020;**18**:173. doi:10.1186/s12916-020-01626-6

11 UNFPA. Zambia - Overview. United Nations Population Fund, Geneva; 2020.

12 UNAIDS. Country factsheets - Zambia 2019. Joint United Nations Programme on HIV/AIDS, Geneva; 2020. https://www.unaids.org/en/regionscountries/countries/zambia

13 Kapata N, Chanda-Kapata P, Ngosa W, *et al.* The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. *PLoS ONE* 2016;**11**:e0146392-14. doi:10.1371/journal.pone.0146392

14 The National Tuberculosis and Leprosy Program. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in Zambia. 2017.

15 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. World Health Organization, Geneva; 2017. https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1

16 Challenge TB. Rapid Scale-Up of New Drugs and Regimens for the Treatment of Drug-Resistant TB in Zambia. FHI 360 Zambia Office, Lusaka 2020.

17 Zambia Ministry of Health. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection: 2018. Available at: http://www.hivst.org/files1/Final-Zambia-Consolidated-Guidelines_2018-Print.pdf.

18 World Health Organization. Global Tuberculosis Report 2019. World Health Organization, Geneva; Published Online First: 2019.https://www.who.int/tb/publications/global_report/en/

19 P Glaziou, C Sismanidis, PJ Dodd, M Zignol, K Floyd. Methods used by WHO to estimate the global burden of TB disease. World Health Organization, Geneva; 2018. 2016.

20 Organization WH. Tuberculosis data. https://www.who.int/teams/global-tuberculosis-programme/data

21 Kapata N, Mbulo G, Cobelens F, *et al.* The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Tropical Medicine & International Health* 2015;**20**:1492–500. doi:10.1111/tmi.12581

22 Holmes CB, Sikazwe I, Sikombe K, *et al.* Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. *PLOS Med* 2018;**15**:e1002489. doi:10.1371/journal.pmed.1002489

23 Zambia Statistics Agency, Ministry of Health (MOH) Zambia, and ICF. 2019. Zambia Demographic and Health Survey 2018. Lusaka, Zambia, and Rockville, Maryland, USA: Zambia Statistics Agency, Ministry of Health, and ICF.

24 Horne DJ, Kohli M, Zifodya JS, *et al.* Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Db Syst Rev* Published Online First: 2019. doi:10.1002/14651858.cd009593.pub4

25 Boehme CC, Nicol MP, Nabeta P, *et al.* Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug

resistance: a multicentre implementation study. *The Lancet* 2011;**377**:1495–505. doi:10.1016/s0140

26 Steingart KR, Henry M, Ng V, *et al.* Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006;**6**:570–81. doi:10.1016/s1473-3099(06)70578-3

27 Organization WH. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. World Health Organization, Geneva; 2016. http://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1

28 Tortoli E, Benedetti M, Fontanelli A, *et al.* Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *Journal of Clinical Microbiology* 2002;**40**:607–10. doi:10.1128/jcm.40.2.607-610.2002

29 WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization, Genevea; 2014.

30 Dye C. Breaking the law: tuberculosis disobeys Styblo's rule. *B World Health Organ* 2008;**86**:4–4. doi:10.2471/blt.07.049510

31 Horton KC, MacPherson P, Houben RMGJ, *et al.* Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002119. doi:10.1371/journal.pmed.1002119

32 Reid MJA, Arinaminpathy N, Bloom A, *et al.* Building a tuberculosis-free world: The Lancet Commission on tuberculosis. *Lancet* 2019;**393**:1331–84. doi:10.1016/s0140-6736(19)30024-8

33 Subbaraman R, Jhaveri T, Nathavitharana RR. Closing gaps in the tuberculosis care cascade: an action-oriented research agenda. *J Clin Tuberc Other Mycobact Dis* 2020;**19**:100144. doi:10.1016/j.jctube.2020.100144

34 Vries SG de, Cremers AL, Heuvelings CC, *et al.* Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. *The Lancet Infectious Diseases* 2017;**17**:e128–43. doi:10.1016/s1473-3099(16)30531-x

35 Krishnan L, Akande T, Shankar AV, *et al.* Gender-Related Barriers and Delays in Accessing Tuberculosis Diagnostic and Treatment Services: A Systematic Review of Qualitative Studies. *Tuberc Res Treat* 2014;**2014**:1–14. doi:10.1155/2014/215059

36 Daniels B, Dolinger A, Bedoya G, *et al.* Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. *Bmj Global Heal* 2017;**2**:e000333. doi:10.1136/bmjgh-2017-000333

37 Kwan A, Daniels B, Saria V, *et al.* Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. *Plos Med* 2018;**15**:e1002653. doi:10.1371/journal.pmed.1002653

38 Sylvia S, Xue H, Zhou C, *et al.* Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. *Plos Med* 2017;**14**:e1002405. doi:10.1371/journal.pmed.1002405

39 Kranzer K, Afnan-Holmes H, Tomlin K, *et al.* The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013;**17**:432–46. doi:10.5588/ijtld.12.0743

40 Partnership ST. Finding the Missing People with TB in Communities. Stop TB Partnership, Geneva; 2018. https://stoptb-strategicinitiative.org/elearning/wp-content/uploads/2019/04/STBFG_03.pdf

41 Marks GB, Nguyen NV, Nguyen PTB, *et al.* Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New Engl J Med* 2019;**381**:1347–57. doi:10.1056/nejmoa1902129

42 Kerkhoff AD, Muyoyeta M, Cattamanchi A. Community-wide Screening for Tuberculosis. *New Engl J Med* 2020;**382**:1185–6. doi:10.1056/nejmc1916666

43 Shapiro AE, Chakravorty R, Akande T, Lonnroth K , Golub JE. A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. World Health Organization, Geneva; 2013.

44 STOP TB. Intensified TB Case Finding at Facility Level. Stop TB Partnership, Geneva; 2018.

45 Hanrahan CF, Nonyane BAS, Mmolawa L, *et al.* Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). *PLOS Med* 2019;**16**:e1002796. doi:10.1371/journal.pmed.1002796

46 Kagujje M, Chilikutu L, Somwe P, *et al.* Active TB case finding in a high burden setting; comparison of community and facility-based strategies in Lusaka, Zambia. *PLoS ONE* 2020.

47 MacPherson P, Houben RM, Glynn JR, *et al.* Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bulletin of the World Health Organization* 2013;**92**:126–38. doi:10.2471/blt.13.124800

48 Thomas BE, Suresh C, Lavanya J, *et al.* Understanding pretreatment loss to follow-up of tuberculosis patients: an explanatory qualitative study in Chennai, India. *Bmj Global Heal* 2020;**5**:e001974. doi:10.1136/bmjgh-2019-001974

49 Dorman SE, Schumacher SG, Alland D, *et al.* Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *The Lancet Infectious Diseases* 2018;**18**:76–84. doi:10.1016/s1473-3099(17)30691-6

50 Alipanah N, Jarlsberg L, Miller C, *et al.* Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *Plos Med* 2018;**15**:e1002595. doi:10.1371/journal.pmed.1002595

51 World Health Organization. A patient-centered approach to TB care. World Health Organization, Geneva; 2018.

52 WHO. WHO policy on collaborative TB/HIV activitiesGuidelines for national programmes and other stakeholders. 2012;**available at: http://apps.who.int/iris/bitstream/10665/44789/1/9789241503006_eng.pdf?ua=1**:1–36.http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf

53 Kerkhoff AD, Cattamanchi A. HIV and Tuberculosis. 2019;:127–59. doi:10.1007/978-3-030-29108-2_7

54 World Health Organization. Systematic screening for active tuberculosis: principles and recommendations. World Health Organization, Geneva; Published Online First: 2013.http://www.who.int/tb/publications/Final_TB_Screening_guidelines.pdf

55 Organization WH. WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. World Health Organization, Geneva; 2017. http://apps.who.int/iris/bitstream/handle/10665/254792/WHO-HTM-TB-2017.04-eng.pdf?sequence=1

56 Organization WH. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019. World Health Organization, Geneva; 2019. 2019.

57 Subbaraman R, Mondesert L de, Musiimenta A, *et al.* Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *Bmj Global Heal* 2018;**3**:e001018. doi:10.1136/bmjgh-2018-001018

58 Kanters S, Park JJH, Chan K, *et al.* Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet Hiv* 2017;**4**:e31–40. doi:10.1016/s2352-3018(16)30206-5

59 Dowdy DW, Theron G, Tornheim JA, *et al.* Drug-resistant tuberculosis in 2017: at a crossroads. *Lancet Respir Medicine* 2017;**5**:241–2. doi:10.1016/s2213-2600(17)30081-4

60 Dheda K, MD PTG, MMed PGM, *et al.* The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *The Lancet Respiratory* 2017;**5**:291–360. doi:10.1016/s2213-2600(17)30079-6

61 Organization WH. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. World Health Organization, Geneva; 2014.

62 Kendall EA, Sahu S, Pai M, *et al.* What will it take to eliminate drug-resistant tuberculosis? *Int J Tuberc Lung Dis* 2019;**23**:535–46. doi:10.5588/ijtld.18.0217

63 Stop TB. TB Impact Measurement. Stop TB Partnership, Geneva; 2012. https://apps.who.int/iris/bitstream/handle/10665/44231/9789241598828_eng.pdf;jsessionid=42D69576966C34CFA9B02841282CCB26?sequence=1

64 Horton KC, Sumner T, Houben RMGJ, *et al.* A Bayesian Approach to Understanding Sex Differences in Tuberculosis Disease Burden. *Am J Epidemiol* 2018;**187**:2431–8. doi:10.1093/aje/kwy131

65 Chikovore J, Hart G, Kumwenda M, *et al.* 'For a mere cough, men must just chew Conjex , gain strength, and continue working': the provider construction and tuberculosis care-seeking implications in Blantyre, Malawi. *Global Health Action* 2015;**8**:26292. doi:10.3402/gha.v8.26292

66 Chikovore J, Hart G, Kumwenda M, *et al.* TB and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2017;**21**:26–33. doi:10.5588/ijtld.16.0925

67 Chanda-Kapata P, Kapata N, Masiye F, *et al.* Health Seeking Behaviour among Individuals with Presumptive Tuberculosis in Zambia. *PLoS ONE* 2016;**11**:e0163975-11. doi:10.1371/journal.pone.0163975

Figure Legend

Figure 1. The tuberculosis care cascade in Zambia in 2018 among: (a) all tuberculosis cases; (b) drug-susceptible cases; (c) rifampicin-resistant cases; (d) drug-susceptible cases among HIV-positive individuals; (e) drug-susceptible cases among HIV-negative individuals**.**

Figure 2. Diagnoses and notifications of (a) all forms of drug-susceptible pulmonary tuberculosis in Zambia between 2015 and 2018, and (b) drug-resistant tuberculosis in Zambia between 2015 and 2018.

Figure 3. Overview of drug-susceptible tuberculosis treatment outcomes in Zambia between 2015 and 2018, disaggregated according to tuberculosis-type. Shapes represent the proportion of patients completing tuberculosis treatment.

Supporting information

Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV status.

Table 1. Approach to and data sources for estimating each step of the tuberculosis care cascade in Zambia in 2018.

	Step 1. TB burden	Step 2. Accessed tests	Step 3. Diagnosed	Step 4. Notified and treated	Step 5. Successfully treated
All TB cases	WHO estimates of TB incidence in 2018 plus 50% of the number of undetected cases from 2017 [18,20].	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV status (informed by published reports [24–26]), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual level data from 4 Zambian provinces in 2017).	Back calculated from number of cases notified (step 4) and proportion of patients lost-to-follow-up prior to initiation of TB therapy (PTLTFU). PTLTFU estimated based on difference between number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 [unpublished]) and number of microbiologically confirmed DS PTB cases notified (informed by aggregated facility-level TB notification data from 2018 [unpublished]).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Add DS-TB and RR-TB cases successfully treated.
Rifampicin-resistant TB cases	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance (informed by most recent Zambia National TB drug resistance survey in 2008 [21]).	Back calculated from RR-TB cases diagnosed (step 3) on the basis of cases bacteriologically diagnosed, by test type and test sensitivity (informed by published reports [24,27,28]).	Exact value from aggregated facility-level TB laboratory data from 2018 (unpublished).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases, all cases	Overall TB burden minus RR-TB cases.	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV status (informed by published reports [24–26]), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual level data from 4 Zambian provinces in 2017).	Back calculated from number of DS-TB cases notified (step 4) and proportion of patients lost-to-follow-up prior to initiation of TB therapy (PTLTFU). PTLTFU estimated based on difference between number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 [unpublished]) and number of microbiologically confirmed DS PTB cases notified (informed by aggregated facility-level TB notification data from 2018 [unpublished]).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases,	WHO 2019 analysis of DS-TB incidence in 2017 plus 50% of the	Add the number of missed cases of DS-TB among HIV-positive individuals to the	Back calculated from number of cases notified (step 4) and proportion of patients lost-to-	Exact value from aggregated facility-level TB notification	Exact value from aggregated facility-level TB treatment outcomes data from 2018

HIV-positive individuals	number of undetected cases from 2018 [18,20].	total number of DS-TB cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated ([24,25]).	follow-up prior to initiation of TB therapy (PTLTFU) [PTLTFU assumed to be the same independent of HIV status].	data from 2018 adjusted for the proportion of patients without an HIV test. (unpublished).	(number successfully treated) adjusted for proportion of patients without an HIV test (unpublished).
Drug-susceptible TB cases, HIV-negative individuals	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals.	Total number of DS-TB cases who accessed TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals.	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals.	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified.	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated.

Table 2. Overview of the tuberculosis care cascade in Zambia in 2018 according to type.

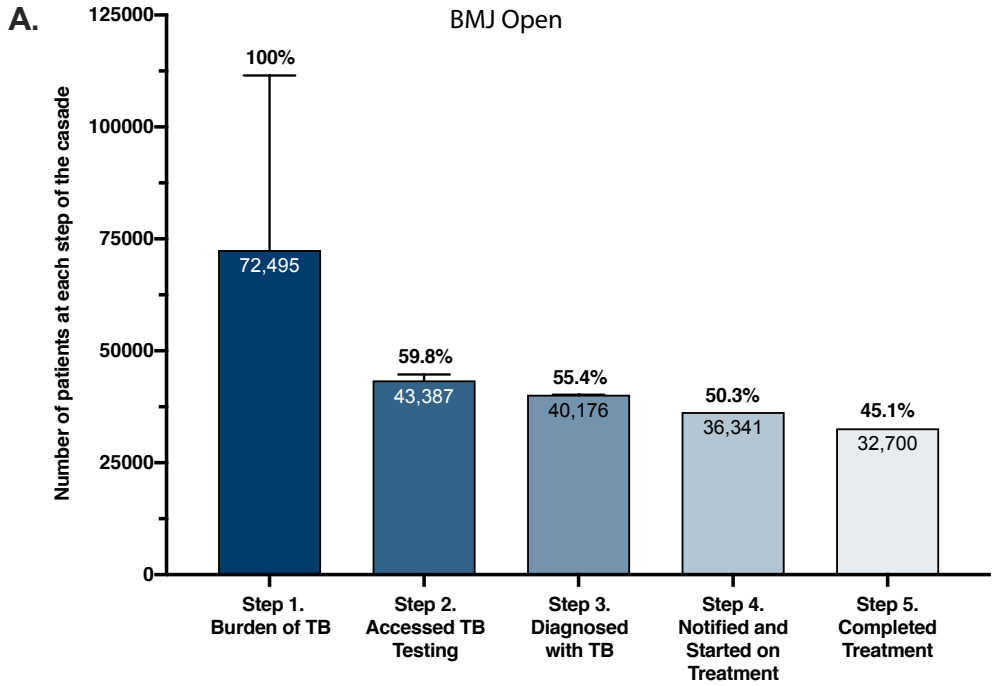
	Step 1. TB burden		Step 2. Accessed tests			Step 3. Diagnosed			Step 4. Notified and treated			Step 5. Successfully treated		
	Cases, range*	Proportion (%)	Cases, range*	Proportion (%)		Cases, range*	Proportion (%)		Cases, range*	Proportion (%)		Cases, range*	Proportion (%)	
Overall TB Cascade	72,495 (40,495-111,495)	100	43,387 (95%CI: 42,390-44,710)	59.8	59.8	40,176 (95%CI: 40,128-40,212)	55.4	92.6	36,431	50.2	90.7	32,700	45.1	89.8
Rifampin-resistant TB	1,740 (486-4,014)	100	910 (95%CI: 776-1,093)	52.3	52.3	627	36.0	68.9	509	29.3	81.2	396396	22.8	77.8
DS-TB, all	70,755 (40,009-107,481)	100	42,477 (95%CI: 41,614-43,625)	60.0	60.0	39,549 (95%CI: 39,501-39,585)	55.9	93.1	35,922	50.8	90.8	32,304	45.7	89.9
DS-TB, HIV-positive	43,411 (23,911-65,911)	100	24,746 (95%CI: 24,290-25,349)	57.0	57.0	23,133 (95%CI: 23,106-23,154)	53.3	93.5	21,012 (95%CI: 20,962-21,064)	48.4	90.8	18,579 (95%CI: 18,535-18,625)	42.8	88.4
DS-TB, HIV-negative	27,344 (16,098-41,570)	100	17,731 (95%CI: 17,324-18,276)	64.8	64.8	16,415 (95%CI: 16,395-16,431)	60.0	92.6	14,910 (95%CI: 14,858-14,960)	54.5	90.8	13,725 (95%CI: 13,679-13,769)	50.2	92.1

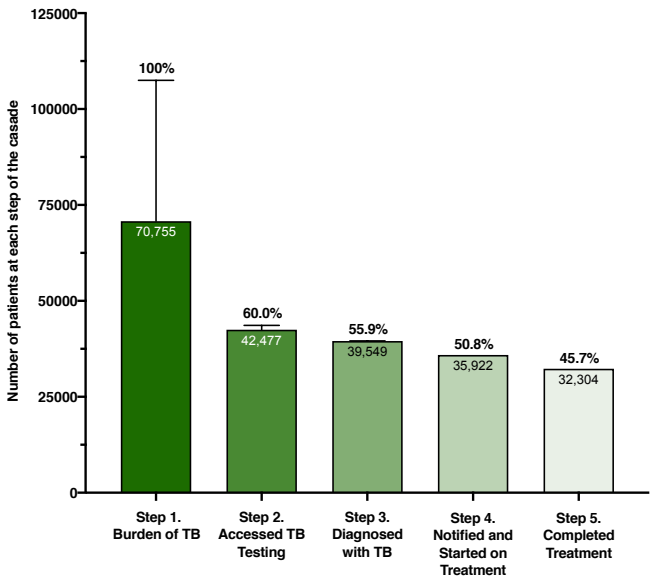
*Values in parentheses represent ranges, unless explicitly specified as 95% confidence intervals. The left-side column under 'proportion' denotes the proportion of TB cases relative to the total TB burden, while the right-side column denotes the proportion of TB cases relative to the prior step in the cascade.

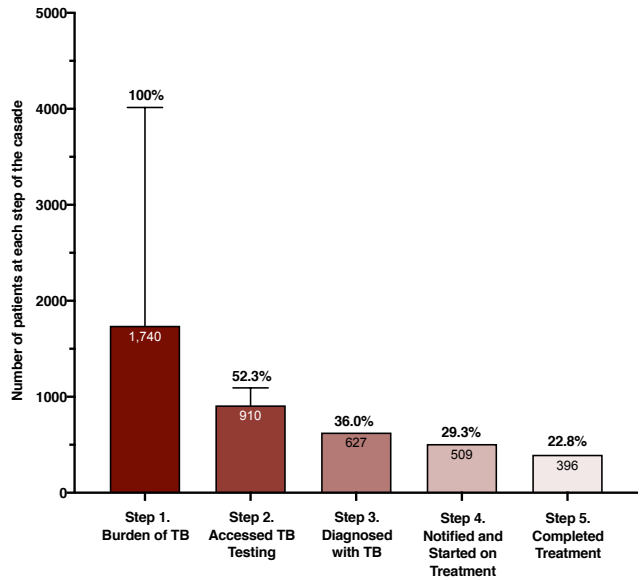
Table 3. Gap analysis of the tuberculosis care cascade in Zambia in 2018 according to type.

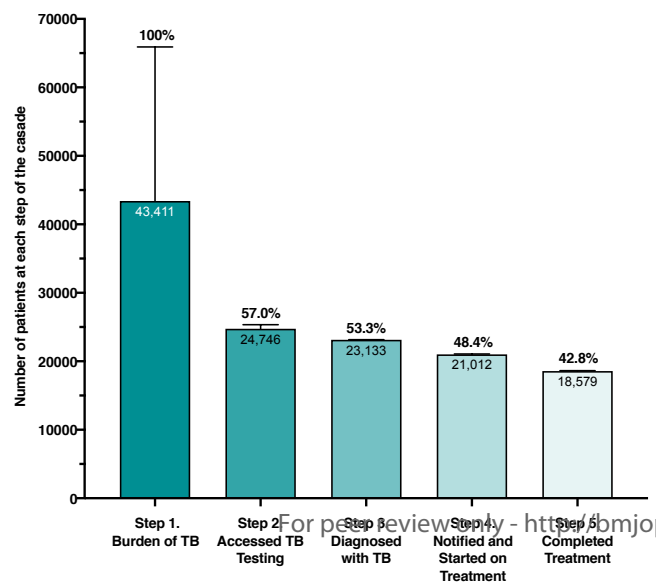
	Overall TB cases lost throughout the care cascade		Gap 1. Patient did not seek care at TB facility and/or have TB tests sent		Gap 2. TB tests sent, but TB missed*		Gap 3. TB diagnosed but patient not started on TB treatment and/or not notified		Gap 4. TB treatment started, but not completed	
	Cases, range*	Proportion (%)	Cases, range*	Proportion (%)	Cases, range*	Proportion (%)	Cases, range*	Proportion (%)	Cases, range*	Proportion (%)
Overall TB Cascade	39,795 (8,191-79,191)	100	29,108 (0-66,777)	73.1	3,211 (95%CI: 2,262-4,506)	8.1	3,745 (95%CI: 3,697-3,781)	9.4	3,731	9.4
Rifampin-resistant TB	1,344 (486-4,014)	100	830 (0-2,921)	61.7	283 (95%CI: 149-466)	21.1	118	8.8	113	8.4
Drug-sensitive TB	38,451 (40,009-107,481)	100	28,278 (0-63,856)	73.5	2,928 (95%CI: 2,112-4,040)	7.6	3,627 (95%CI: 3,579-3,663)	9.4	3,618	9.4
HIV-positive, drug-sensitive TB	24,832 (5,376-47,286)	100	18,597 (0-40,495)	75.2	1,613 (95%CI: 1,185-2,194)	6.5	2,121 (95%CI: 2,094-2,142)	8.5	2,379 (95%CI: 2,337-2,529)	9.8
HIV-negative, drug-sensitive TB	13,619 (2,419-27,801)	100	10,939 (98-24,620)	70.6	1,315 (95%CI: 927-1,846)	9.7	1,505 (95%CI: 1,486-1,520)	11.1	1,239 (95%CI: 1,089-1,281)	8.7

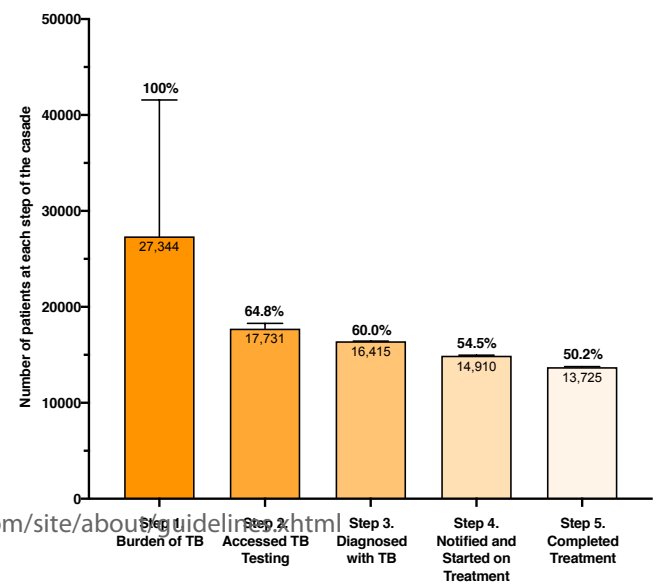
*Values in parentheses represent ranges, unless explicitly specified as 95% confidence intervals. Proportions are relative to the total number of TB cases estimated to have been lost throughout the care cascade. For rifampicin resistant TB, either the TB diagnosis or the rifampicin resistance was missed.



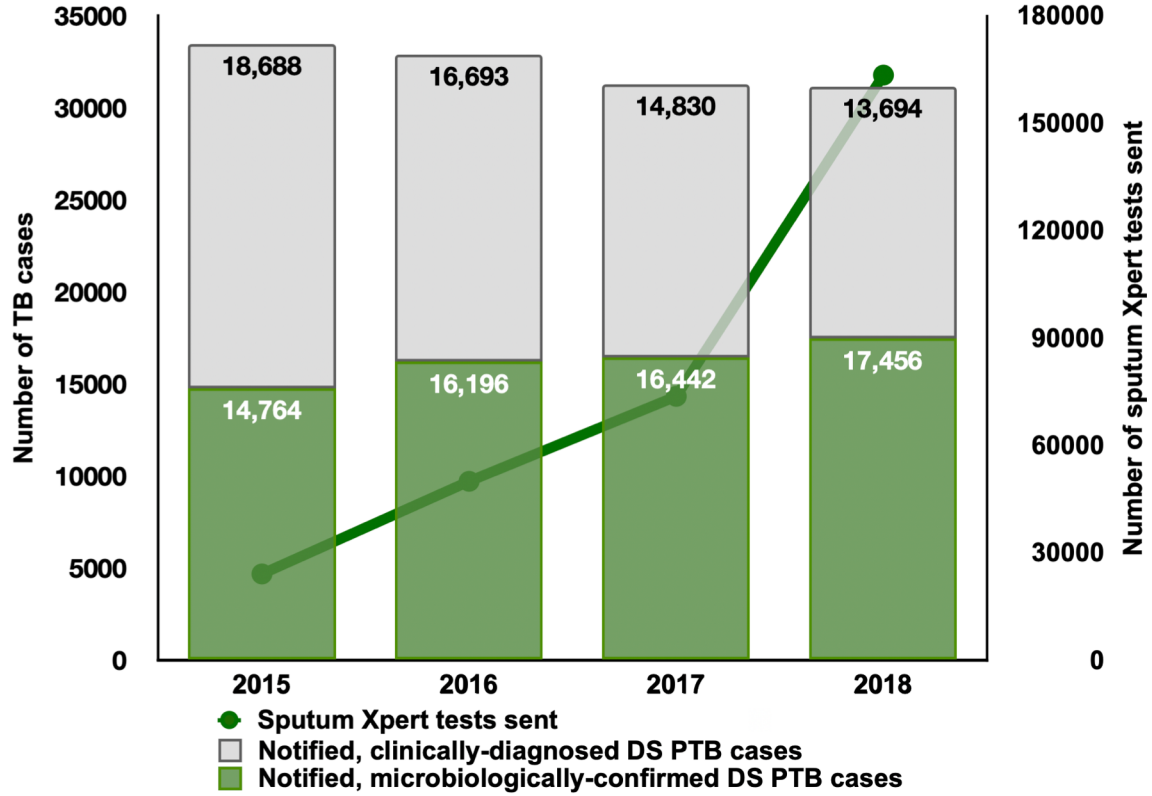




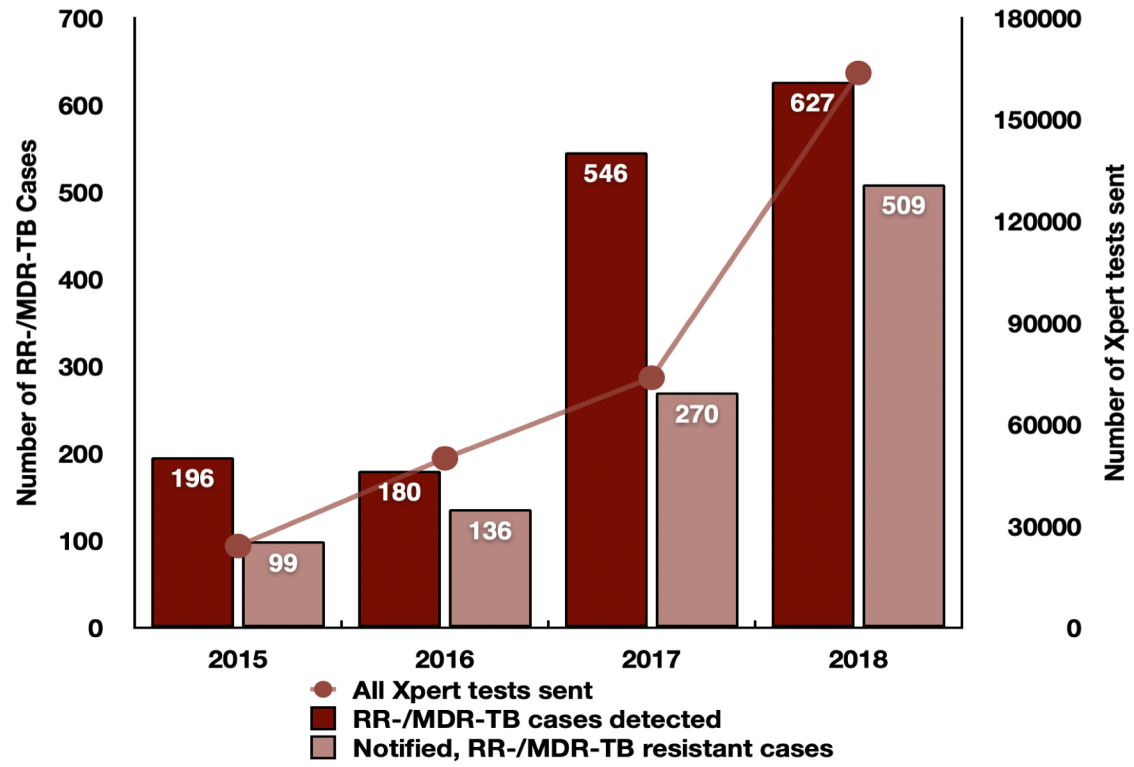


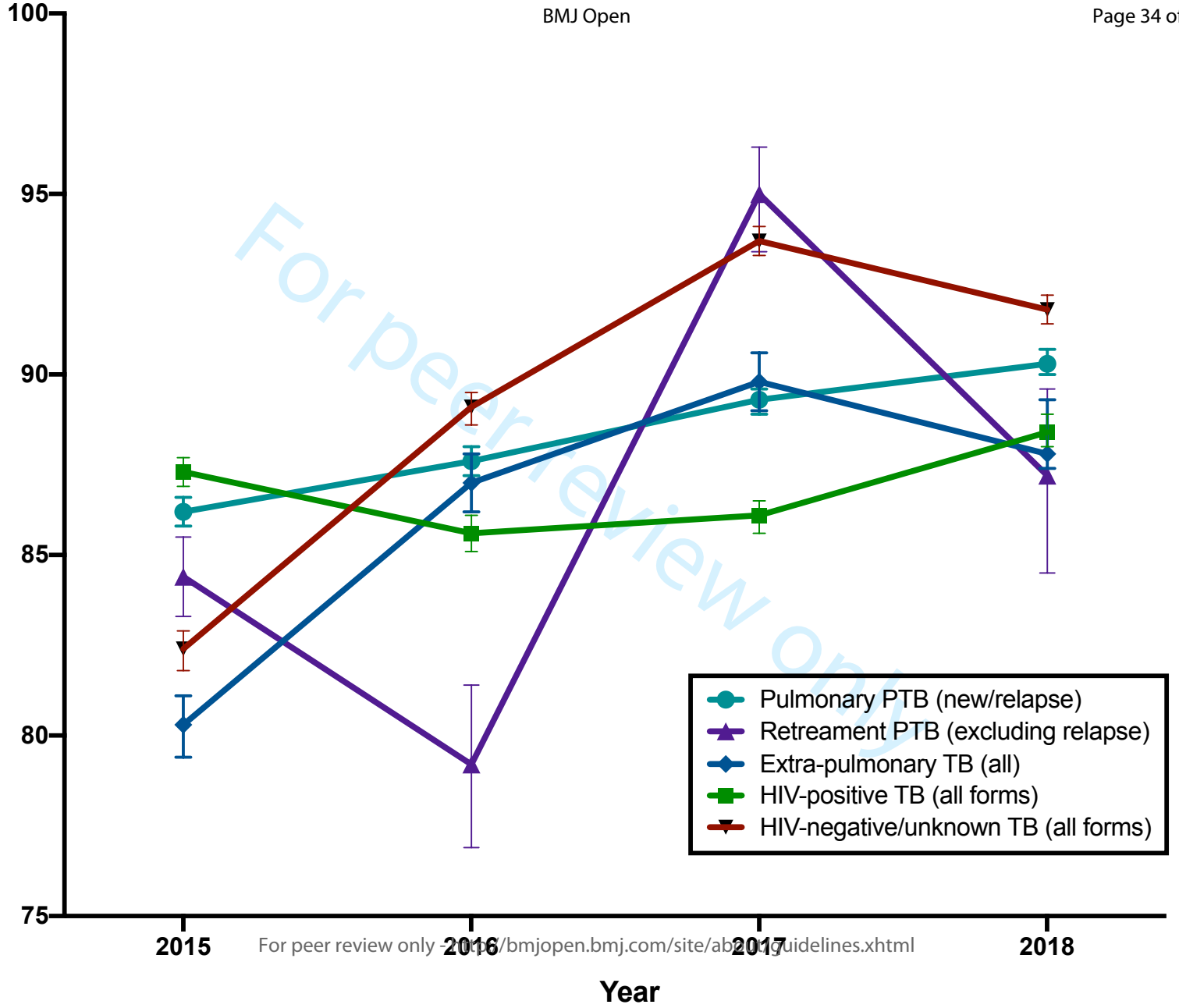


A.


35000
30000
25000
20000
15000
10000
5000
0
Number of TB cases
180000
150000
120000
90000
60000
30000
0
Number of sputum Xpert tests sent
18,688
16,693
14,830
13,694
14,764
16,196
16,442
17,456
2015
2016
2017
2018
Sputum Xpert tests sent
Notified, clinically-diagnosed DS PTB cases
Notified, microbiologically-confirmed DS PTB cases

B.


700
600
500
400
300
200
100
0
Number of RR-/MDR-TB Cases
180000
150000
120000
90000
60000
30000
0
Number of Xpert tests sent
196
99
180
136
546
270
627
509
2015
2016
2017
2018
All Xpert tests sent
RR-/MDR-TB cases detected
Notified, RR-/MDR-TB resistant cases



Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Table 1. Overall TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. TB burden	72,495 (40,495 - 111,495)	100	WHO 2019 analysis of TB incidence in 2018 plus 50% of the number of undetected cases from 2017.[1]	• TB incidence, 2018 (all): 60,000 • TB incidence, 2017 (all): 61,000 • Case detection rate, 2017: 59.0% • Estimated undetected cases 2017: 24,990 • 50% of undetected cases who have not died/self-cured: 12,495
Gap 1	29,108 (0-66,777)	40.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	43,387 (95%CI: 42,390-44,718)	59.8	Add DS-TB and RR-TB cases that accessed TB testing (see Tables 2 and 3 for estimates).	• DS-TB: 42,477 (95%CI: 41,614-43,625) • RR-TB: 910 (95%CI: 776-1,093)
Gap 2	3,211 (95%CI: 2,262-4,506)	4.4	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed	40,176 (95%CI: 40,128-40,212)	55.4	Add DS-TB and RR cases diagnosed (see Tables 2 and 3 for estimates).	• DS-TB: 39,549 (95%CI: 39,501-39,585) • RR-TB: 627
Gap 3	3,745 (95%CI: 3,697-3,781)	5.2	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated	36,431	50.2	Add DS-TB and RR cases notified and treated (see Tables 2 and 3 for estimates).	• DS-TB: 35,922 • RR-TB: 509
Gap 4	3,731	5.1	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated	32,700	45.1	Add DS-TB and RR cases successfully treated (see Tables 2 and 3 for estimates).	• DS-TB: 32,304 • RR-TB: 396

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 2a. Drug-susceptible TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	70,755 (40,009-107481)	100	Overall TB burden minus RR-TB cases.	• TB burden: 72,495 (40,495-111,495) • RR cases: 1740 (486-4014)
Gap 1	28,278 (0-63,856)	40.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	42,477 (95%CI: 41,614-43,625)	60.0	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV-status, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 39,549 (95%CI: 39,501-39,585) • Number missed: 2,928 (95%CI: 2,112-4,040)
Gap 2	2,928 (95%CI: 2,112-4,040)	4.1	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	39,549 (95%CI: 39,501-39,585)	55.9	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy. PTLTFU estimated based on difference between number of microbiologically confirmed DS PTB cases detected and number of microbiologically confirmed DS PTB cases notified (Table 2c).	• PTLTFU estimate: = 9.2 (95%CI: 9.1-9.3) • Number of patients notified in 2018: 35,922
Gap 3	3,627 (95%CI: 3,579-3,663)	5.1	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	35,922	50.8	Exact value from aggregated facility-level TB notification data.	• All patients with DS-TB who were notified and started on treatment (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).
Gap 4	3,618	5.1	Step 4 estimated cases minus Step 5 estimated cases	
Step 5. Successfully treated for TB.	32,304	45.7	Exact value from aggregated facility-level TB treatment outcomes data.	• All patients with DS-TB who successfully completed TB therapy (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).

Table 2b. Estimation method for determining number of patients with DS-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall
Total number of all microbiologically-confirmed TB cases (who therefore underwent microbiological tests)[1]	8,025 (PTB) + 320 (EPTB) = 8,345	9,803 (PTB)+1,137 (EPTB) = 10,940	19,285
Number of the above who underwent Xpert[1]	7,320	9,071	16,391
Number who underwent smear[1]	1,025	1,869	2,894
Proportion who underwent smear only (were smear-positive but Xpert either not done, or negative)[2]	96.9% (95%CI: 95.6-98.0)	98.1% (95%CI: 97.1-98.8)	97.7% (95%CI:96.9-98.3)
Number who underwent smear only	1,025 x .969% (95%CI: .956-.980) = 993 (95%CI: 980-1,005)	1,869 x .981% (95%CI: .971-.988) = 1,833 (95%CI: 1815-1,847)	-
Sensitivity of Xpert[3]	81% (95%CI 75-86)	88% (95%CI: 83-92)	85% (95%CI: 82-88)
Cases missed by Xpert	7,320/ .81 (95%CI .75-.86) - 7,320 = 1,717 (95CI: 1,192-2,440)	9,071 /.88 (95%CI: .83-.92)- 9,071 = 1,237 (95%CI: 789-1,858)	2,594 (95%CI: 1,980-4,298)
Sensitivity of smear microscopy[4,5]	50% (95%CI:42-57)	76% (95%CI: 70-80)	-
Cases missed by smear	993/0.50 (95%CI:0.42-0.57)- 993 = 1,025 (95%CI: 773-1,415)	1,833/0.76 (0.70-0.80)-1,833 = 590 (95%CI: 467-801)	1,615 (95%CI: 1,240-2,216)
Total combined cases missed by Xpert and smear	2,472 (95CI: 1,965-3,855)	1,827 (95%CI: 1,256-2,659)	4,569 (95%CI: 3,221-6,514)
Proportion of patients who had a negative Xpert that were empirically treated[2]	30.6% (95%CI: 28.6-32.7)	22.7% (95%CI:19.8-25.9)	28.9 (95%CI: 27.2-30.6)
Negative Xpert / received empiric therapy	1,717 (95CI: 1,192-2,440) x .306 (95%CI: .286-.327) = 525 (95: 341-798)	1,237 (95%CI: 789-1,858) x .227 (95%CI:.198-259) = 281 (95%CI: 156-481)	806 (95%CI: 497-1,279)

Proportion of patients who had a negative smear that were empirically treated[2]	58.9% (95%CI: 56.8-61.0)	39.2% (95%CI: 36.9-41.4)	50.1 (95%CI 48.5-51.6)
Negative smear / received empiric therapy	1,025 (95%CI: 773-1,415) x .589 (95%CI: .568-.610) = 604 (95%CI: 439-863)	590 (95%CI: 467-801) x .392% (95%CI: .369-.414) = 231 (95%CI: 172-332)	835 (95%CI: 612-1,195)
Total cases that were negative by Xpert or smear that were empirically treated	1,129 (95%CI: 780-1,661)	529 (95%CI: 329-813)	1,641 (95%CI: 1,109-2,474)
Total Missed cases (Total number of cases missed by Xpert or smear minus those were empirically treated)	1,613 (95%CI: 1,185-2,194)	1,315 (95%CI: 927-1,8460	2,928 (95%CI: 2,112-4,040)

[1]Exact value from 2018 national TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished), [3]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593.[4]Estimate from: Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 377:1495–505. [5]Estimate from: Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:570–81.

Table 2c. Estimation method for determining proportion of patients with pre-treatment lost-to-follow-up.

Variable	Overall
Unadjusted number of microbiologically-confirmed pulmonary TB cases[1]	19,285 (16,391 Xpert and 2,894 smear)
Proportion of patients with positive smear who also have a positive Xpert result[2]	2.3% (95%CI 1.7-3.1)
Number of patients with positive smear who also have a positive Xpert result[2]	2,894 x .023% (95%CI .017-.031) = 67 (95%CI: 49-90)
Adjusted number of microbiologically-confirmed PTB cases	(2,894 - 67 (95%CI: 49-90)) + 19,218 (95%CI: 19,195-19,236)
Number of patients with microbiologically-confirmed pulmonary TB notified in 2018[3]	17,456
Proportion of all patients with microbiologically-confirmed TB who were registered and started TB treatment	90.8 (95%CI: 90.7-90.9)
Pre-treatment lost-to-follow-up (PTLTFU) estimate:	100% - 90.8 (95%CI: 90.7-90.9) = 9.2% (95%CI: 9.1-9.3)

[1]Exact value from 2018 nationally aggregated TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished).[3]Exact value from 2018 nationally aggregated TB notification register.

Table 3. Rifampicin resistant TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	1,740 (486-4,014)	100	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance.	• TB burden: 72,495 (40,495-111,495) • Overall estimate of RR-TB: 2.4% (95CI: 1.2-3.6)[1]
Gap 1	830 (range, 0-2,921)	47.7	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	910 (95%CI: 776-1,093)	52.3	Back calculated from RR tuberculosis cases diagnosed on the basis of cases bacteriologically diagnosed, by test type and test sensitivity.	• RR-TB cases diagnosed: 627 • RR-TB cases missed: 283
Gap 2	283 (95%CI: 149-466)	16.3	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	627	36.0	Exact value from aggregated facility-level TB laboratory data.	• All patients with microbiologically-confirmed RR-TB
Gap 3	118	6.8	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	509	29.3	Exact value from aggregated facility-level TB notification data.	• All patients with RR-TB who were notified and started on treatment.
Gap 4	113	6.5	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	396	22.8	Exact value from aggregated facility-level TB treatment outcomes data.	• The number of RR-TB who were notified and started on treatment who were successfully treated.

[1]Estimate from: Kapata N, Mbulo G, Cobelens F, et al. The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health*. 2015;20(11):1492-1500. This is the most recent Zambia national drug resistance survey. A higher estimate utilizing MDR-TB Plus chosen because it more closely coincides with WHO RR-TB incidence estimates for 2018.

Table 3b. Estimation method for determining number of patients with RR-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall, No
Number of laboratory-confirmed RR-cases	-	-	627
Proportion of RR-TB patients notified in 2018, by HIV-status.[1]	59.1% (95CI: 54.6-63.6)	40.9% (95%CI: 36.4-45.4)	-
Number of RR-TB patients diagnosed in 2018, by HIV-status	627 x 59.1% (95CI: 54.6-63.6) = 371 (95%CI: 342-399)	627 x 40.9% (95%CI: 36.4-45.4) = 256 (95%CI: 228-285)	627
Number of RR-cases detected by Xpert	-	-	372
Number of RR-cases detected by Xpert, by HIV-status	372 x 59.1% (95CI: 54.6-63.6) = 220 (95%CI: 203-237)	372 x 40.9% (95%CI: 36.4-45.4) = 152 (95%CI: 135-169)	372
Combined sensitivity of Xpert for Rif-Resistance, by HIV status[2]	• Sensitivity of Xpert for TB: 81% (95%CI: 75% to 86%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RR-TB: 77.8% (95%CI 70.5-83.4)	• Sensitivity of Xpert for TB: 88% (95%CI: 83% to 92%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RIF-resist TB: 84.5% (95%CI 78.0-89.2)	-
RR-cases missed by Xpert	220 (95%CI: 203-237)/ .778 (95%CI .705-.834) – 220 = 63 (95%CI: 24-116)	152 (95%CI: 135-169)/ .845 (95%CI .780-.892) – 152 = 28 (95%CI: 0-64)	91 (95%CI: 23-180)
Number of RR-cases detected by MDR-TB plus	-	-	135
Number of RR-cases detected by MDR-TB plus, by HIV-status	135 x 59.1% (95CI: 54.6-63.6) = 80 (95%CI: 74-86)	135 x 40.9% (95%CI: 36.4-45.4 = 55 (95%CI: 49-61)	135
Combined sensitivity of MDR-TB plus*[3]	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 48.5% (95%CI: 40.1-55.9)	• Sensitivity of smear for TB: 76% (95%CI: 70-80) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 73.6% (95%CI: 66.9-78.4)	-
RR-cases missed by MDR-TB plus	80 (95%CI: 74-86) /.485 (95%CI: .401-.559) - 80 = 85 (95%CI: 52-134)	55 (95%CI: 49-61) / .736 (95%CI: .669-.784) - 55 = 20 (95%CI: 7-36)	105 (95%CI: 59-171)

Number of RR-cases detected by liquid culture (MGIT 960)*[4]			120
Number of RR-cases detected by liquid culture (MGIT 960)*[4], by HIV-status	120 x 59.1% (95CI: 54.6-63.6) = 71 (95%CI: 66-76)	120 x 40.9% (95%CI: 36.4-45.4 = 49 (95%CI: 44-54)	120
Combined sensitivity of liquid culture	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 49.6% (40.3-57.0)	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 75.4 (95%CI: 67.1-80.0)	-
RR-cases missed by liquid culture	71 (95%CI: 66-76) / .496 (95%CI: .403-.570) – 71 = 72 (95%CI: 61-83)	43 (95%CI: 49-54) / .754 (95%CI: .671-.800) – 43 = 16 (95%CI: 6-32)	88 (95%CI: 67-115)
Total microbiologically-missed cases	63 (95%CI: 24-116) + 85 (95%CI: 52-134) + 72 (95%CI: 61-83) = 220 (95%CI: 137-333)	28 (95%CI: 0-64) + 20 (95%CI: 7-36) + 16 (95%CI: 6-32) = 64 (95%CI: 13-133)	283 (95%CI: 149-466)
Received empiric therapy*	0	0	0
Total Missed cases	220 (95%CI: 137-333)	64 (95%CI: 13-133)	283 (95%CI: 149-466)

[1]Exact value from 2018 national TB laboratory register. [2]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593. [3]Estimate from: WHO. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Geneva: WHO; 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1, [4]Estimated from: Tortoli E, Benedetti M, Fontanelli A, Simonetti MT. Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Microbiol.* 2002;40(2):607-610.

Table 4. Drug-susceptible TB Care Cascade among HIV-positive individuals in Zambia in 2018

Variable	Cases, range	Proportion (%), range	Estimation method	Calculation
Step 1. Overall TB burden	43,411 (23,911-65,911)	100	WHO 2019 analysis of TB incidence in 2017 plus 50% of the number of undetected cases from 2018.[1]	• TB incidence, 2018 (all): 36,000 (range, 23,000-51,000) • TB incidence, 2017 (all): 36,000 (range, 23,000-51,000) • Case detection rate, 2017: 58.8% (range, 41.5-92.1) • Estimated undetected cases 2017: 14,822 (range, 1,822-29,822) • 50% of undetected cases who have not died/self-cured: 7,411 (range, 911-14,911)
Gap 1	18,597 (0-40,495)	43.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	24,746 (95%CI: 24,290-25,349)	57.0	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 23,133 (95CI: 23,106-23,154) • Number missed (table 2b): 1,613 (95%CI: 1,185-2,194)
Gap 2	1,613 (95%CI: 1,185-2,194)	3.7	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	23,133 (95%CI: 23,106-23,154)	53.3	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy (PTLTFU) [see Table 2c]; [assumed to be the same independent of HIV-status].	• PTLTFU estimate: 9.2% (95%CI: 9.1-9.3) • Number of HIV-positive patients notified in 2018: 21,012 (95%CI: 20,962-21,064)
Gap 3	2,121 (95%CI: 2,094-2,142)	4.9	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	21,012 (95%CI: 20,962-21,064)	48.4	Exact value from aggregated facility-level TB notification data adjusted for proportion of patients without an HIV test.	• DS-TB: 19,332 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

Gap 4	2,433 (95%CI: 2,337-2,529)	5.6	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	18,579 (95%CI: 18,535-18,625)	42.8	Exact value from aggregated facility-level TB treatment outcomes data (number successfully treated) adjusted for proportion of patients without an HIV test.	• DS-TB: 17,624 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 5. Drug-susceptible TB Care Cascade among HIV-negative individuals in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	27,344 (16,098-41,570)	100	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals	• Number of DS-TB cases: 70,755 (range, 40,009-107,481) • Number of HIV-positive DS-TB cases: 43,411 (23,911-65,911)
Gap 1	10,939 (98-24,620)	35.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	17,731 (95%CI: 17,324-18,276)	64.8	Total number of DS-TB cases who accesses TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals	• Number of DS-TB cases that accessed tests: 42,477 (95%CI: 41,614-43,625) • Number of HIV-positive DS-TB cases diagnosed: 24,746 (95%CI: 24,290-25,349)
Gap 2	1,315 (95%CI: 927-1,846)	4.8	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	16,415 (95%CI: 16,395-16,431)	60.0	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals	• Number of DS-TB cases diagnosed: 39,549 (95%CI: 39,501-39,585) • Number of HIV-positive DS-TB cases diagnosed: 23,133 (95%CI: 23,106-23,154)
Gap 3	1,505 (95%CI: 1,486-1,520)	5.5	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	14,910 (95%CI: 14,858-14,960)	54.5	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified	• Number of DS-TB cases notified: 35,922 • Number of HIV-positive DS-TB cases notified: 21,012 (95%CI: 20,962-21,064)
Gap 4	1,185 (95%CI: 1,089-1,281)	4.3	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	13,725 (95%CI: 13,679-13,769)	50.2	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated	• Number of DS-TB cases treated: 32,304 • Number of HIV-positive DS-TB cases treated: 18,633 (95%CI: 18,535-18,725)

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV-status.

	HIV-positive						HIV-negative or unknown HIV status					
	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated
2015	20967	18312 (87.3)	71 (0.3)	1117 (5.3)	682 (3.3)	785 (3.7)	20621	16986 (82.4)	102 (0.5)	1392 (6.8)	1168 (5.7)	973 (4.7)
2016	21655	18541 (85.6)	171 (0.8)	1354 (6.3)	705 (3.3)	884 (4.1)	18498	16481 (89.1)	55 (0.3)	1058 (5.7)	486 (2.6)	418 (2.3)
2017	20362	17527 (86.1)	136 (0.7)	1622 (8.0)	731 (3.6)	346 (1.7)	16841	15779 (93.7)	40 (0.2)	569 (3.4)	135 (0.8)	318 (1.9)
2018	19932	17624 (88.4)	113 (0.6)	1253 (6.3)	521 (2.6)	421 (2.1)	15990	14680 (91.8)	46 (0.3)	745 (4.7)	342 (2.1)	177 (1.1)

BMJ Open

The tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044867.R2
Article Type:	Original research
Date Submitted by the Author:	08-May-2021
Complete List of Authors:	Lungu, Patrick; Zambia Ministry of Health, National Tuberculosis and Leprosy Control Programme; University of Zambia University Teaching Hospital, Department of Internal Medicine Kerkhoff, Andrew; Zuckerberg San Francisco General Hospital and Trauma Center, Division of HIV, Infectious Diseases and Global Medicine Kasapo, Clara; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Mzyece, Judith; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Nyimbili, Sulani; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Chimzizi, Rhehab; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Silumesi, Andrew; Zambia Ministry of Health Kagujje, Mary; Center for Infectious Disease Research in Zambia Subbaraman, Ramnath; Tufts University School of Medicine, Department of Public Health and Community Medicine Muyoyeta, Monde ; Center for Infectious Disease Research in Zambia Malama, Kennedy; Ministry of Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Global health, Health services research
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis

Short title: TB Care Cascade in Zambia

AUTHORS: Patrick S. Lungu[1,2*], Andrew D. Kerkhoff[3*], Clara C. Kasapo[1], Judith Mzyece[1], Sulani Nyimbili[1], Rhehab Chimzizi[1], Andrew Silumesi[4], Mary Kagujje[5], Ramnath Subbaraman[6], Monde Muyoyeta[5], Kennedy Malama[4]

Affiliations:

[1]National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia
[2]Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia
[3]Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco, San Francisco, CA, USA
[4]Ministry of Health, Lusaka, Zambia
[5]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia
[6]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

*PSL and ADK contributed equally.

Corresponding author:
Dr. Patrick S. Lungu
Email: lungupatrick99@gmail.com

Article type: Original article

Keywords: Tuberculosis, care cascade, loss to follow-up, Zambia, HIV, rifampicin resistance

Abstract

Objectives: Tuberculosis (TB) remains a leading cause of morbidity and mortality in Zambia, especially for people living with HIV (PLHIV). We undertook a care cascade analysis to quantify gaps in care and align program improvement measures with areas of need.

Design: Retrospective population-based analysis.

Setting: We derived national-level estimates for each step of the TB care cascade in Zambia. Estimates were informed by WHO incidence estimates, nationally aggregated laboratory and notification registers, and individual-level program data from four provinces.

Participants: All individuals with active TB disease in Zambia in 2018. We characterized the overall TB cascade and disaggregated by drug-susceptibility results and HIV status.

Results: In 2018, the total burden of TB in Zambia was estimated to be 72,495 (range, 40,495-111,495) cases. Of these, 43,387 (59.8%) accessed TB testing, 40,176 (55.4%) were diagnosed with TB, 36,431 (50.3%) were started on treatment and 32,700 (45.1%) completed treatment. Among all persons with TB lost at any step along the care cascade (n=39,795), 29,108 (73.1%) were lost prior to accessing diagnostic services, 3,211 (8.1%) prior to diagnosis, 3,745 (9.4%) prior to initiating treatment, and 3,731 (9.4%) prior to treatment completion. PLHIV were less likely than HIV-negative individuals to successfully complete the care cascade (42.8% vs. 50.2%; p<0.001). Among those with rifampicin-resistant TB, there was substantial attrition at each step of the cascade and only 22.8% were estimated to have successfully completed treatment.

Conclusions: Losses throughout the care cascade resulted in a large proportion of individuals with TB not completing treatment. Ongoing health systems strengthening, and patient-centered engagement strategies are needed at every step of the care cascade; however, scale-up of active case finding strategies is particularly critical to ensure individuals with TB in the population reach initial stages of care. Additionally, a renewed focus on PLHIV and individuals with drug-resistant TB is urgently needed to improve TB-related outcomes in Zambia.

Strengths and limitations of this study

- The national tuberculosis (TB) care cascade for Zambia in 2018 was characterized in order to identify gaps in care.
- The TB care cascade was constructed for all TB patients as well as according to drug-susceptibility result and HIV status.
- The analysis was informed by a published set of methodologies and utilized several data sources to derive estimates.
- Enhanced TB surveillance programs, including the use of unique TB patient identifiers, would allow for real-time monitoring and improved estimates to inform programmatic strengthening.

Background

The WHO End TB strategy aims to reduce tuberculosis (TB) incidence by 90% and TB-related deaths by 95% between 2015 and 2035 [1]. While many high burden countries in sub-Saharan Africa, including Zambia, have demonstrated large reductions in new TB cases and associated mortality, there remains significant need for improved TB care delivery [2]. TB remains a leading cause of morbidity and mortality in Zambia, especially among people living with HIV (PLHIV) [2,3]. In 2019, there were approximately 59,000 new individuals with active TB disease in Zambia (incidence rate of 333 per 100,000 per year) that resulted in 15,400 TB-related deaths, of which 62% were among PLHIV [2]. Despite substantial declines in TB incidence over the last decade, Zambia still has the seventh highest TB incidence in sub-Saharan Africa and remains one of 30 WHO high TB burden priority countries [2].

The HIV "cascade of care" is a public health model that outlines the key engagement steps required for PLHIV to ultimately achieve an undetectable viral load. This model has been widely applied by HIV programs globally to inform and strengthen HIV care and delivery and ultimately, significantly increase the number of PLHIV who know their HIV status, are started on ART and have suppressed viral loads [4]. Similarly, a national TB care cascade can provide key insights to identify and quantify gaps in the diagnosis and care of TB patients that could then help guide programmatic and research priorities by aligning limited resources with the areas of greatest need [5,6]. However, to-date, only three high burden TB countries - South Africa, India, and Madagascar - have undertaken and published national-level TB care cascade analyses [7–9].

We sought to construct a national TB cascade of care for Zambia to evaluate care delivery for individuals with active TB disease through enumeration of gaps in the overall care cascade in 2018 as well as disaggregated by rifampicin susceptibility results and HIV status. Estimates were derived using multiple data sources and the overall approach was informed by a recently published methodology for constructing TB care cascades [6].

Methods

We undertook a retrospective, population-based study to characterize the TB care cascade in Zambia in 2018. All Zambians estimated to be living with TB in 2018 were included in the analysis, regardless of age, HIV status, diagnosis status (i.e., diagnosed or undiagnosed TB), TB drug susceptibility status, or TB-type (i.e., new or retreatment).

Setting

Zambia has an estimated population of 18,400,000 people [10]. It has a high prevalence of HIV (11.5% among adults aged 15-49 years old), and it is estimated that at least 1.2 million persons are living with HIV [11]. TB is a major public health problem in Zambia [3]; during the last national TB prevalence survey conducted in 2013 and 2014, the prevalence of microbiologically-confirmed TB was estimated to be 638 per 100,000 persons and was five-times higher among HIV-positive individuals compared to HIV-negative individuals [12].

Testing and treatment for TB is almost universally provided within Zambia's public health system. While exact estimates are not available, likely <1% of all individuals with TB are detected and managed within Zambia's private sector and the large majority are reported to Zambia's National TB Program (NTP) – this assumption is informed by a national data quality audit conducted in 2019 [13].Within the public health sector, the direct costs of all TB diagnostics and treatment are provided free of charge. In 2018, Xpert MTB/RIF was the recommended first-line diagnostic for all individuals undergoing evaluation for possible TB (pulmonary or extra-pulmonary) in Zambia as well as initial drug-susceptibility testing (DST) [14]; however, it was not universally available at all facilities, in which case routine TB investigations included acid fast bacilli (AFB) fluorescence or Ziehl-Neelsen microscopy and chest radiography, where available. Among those with confirmed rifampicin-resistant (RR) or multidrug-resistant (MDR) TB, it was recommended that either liquid culture or a molecular line probe assay should be used as follow-on tests for further DST [14]. First line TB treatment was provided to all patients without evidence of rifampicin-resistance and consisted of isoniazid, rifampicin, ethambutol and pyrazinamide for 6-9 months in conformity with WHO recommendations [15]. In 2018, Zambia began scaling up shorter treatment regimens comprised of new and repurposed TB drugs for 9-12 months for

eligible RR- and MDR-TB patients – this accounted for the majority of patients [16,17]; however, some patients still received longer MDR-TB treatment regimens comprised of several TB drugs, including an injectable agent, for at least 20 months.

In Zambia, patients diagnosed with TB are notified in a paper-based register and initiated on TB therapy at the corresponding TB treatment facility, which is also responsible for documentation of the treatment outcome of the patient. Data on diagnostic outcomes (laboratory register), notifications and treatment outcomes (notification register) are aggregated from each facility through the district office to the provincial level and then the national level on a monthly basis.

Ethics

Because this was a retrospective, population-level analysis without the use of any patient identifiers, the University of Zambia Biomedical Research Ethics Committee determined that this study met the criteria for exempt-status (REF. 001-02-21).

Patient and public involvement

Patients and the public were not involved in the design and conduct of this analysis. However, there are plans to disseminate the findings to TB communities through TB stakeholder meetings with neighborhood health committees, which includes former TB patients and other community TB advocates.

TB Cascade Data Sources

Several data sources were used to inform estimates within each of the five steps of the care cascade (**Table 1, Supplementary Appendix**). To inform estimates of the overall burden of TB in Zambia in 2018 (Step 1), WHO estimates of TB incidence from 2018 and 2017 were utilized [18–21]**.** The proportion of total individuals with TB estimated to be rifampicin-resistant was derived using estimates from the most recent national survey of TB drug resistance in Zambia [22]; this source was chosen in order to ground estimates of RR-TB in empiric data, however, higher-end estimates from the latest Zambian national survey of TB drug resistance in 2008 were used to more closely align with WHO incidence estimates for RR-TB in 2018. Diagnostic outcomes (Steps 2 and 3) were informed by a nationally aggregated database of TB diagnostics

from 2018, which includes the number and type of investigations (Xpert or smear microscopy) and the number of TB patients detected according to type of TB investigation and HIV status. All treatment outcomes (Steps 4 and 5) were informed by a nationally aggregated TB treatment register from 2018.

Individual level programmatic data from four Zambian Provinces (Eastern, Lusaka, Southern, Western) regarding all patients investigated for TB and those started on treatment between January 1st and December 31st 2017 (n=43,896, n=11,814, respectively) was used to determine: (a) the proportion of patients who had both positive Xpert and smear microscopy results as well as (b) the proportion of patients who were Xpert or smear-negative, but received empirical TB therapy. This helped to further refine estimates for Steps 2 and 3 by accounting for and removing duplicate patients (**Supplementary Appendix**). Patient-level data was only available from 4 out of 10 provinces; however, they account for nearly 60% of Zambia's national TB notifications and the range of socioeconomic characteristics of individuals as well as their access to healthcare services are representative of the other 6 provinces [23,24]. Unfortunately, robust data from 2018 to inform these estimates were unavailable – thus, we utilized 2017 data because it was well-characterized and temporally close to the year for which we sought to characterize the TB care cascade.

Diagnostic sensitivity estimates of Xpert [25] and smear microscopy [26,27] for the detection of TB stratified according to HIV status, as well as Xpert [25], molecular line probe assays [28] and liquid culture [29] for rifampicin-resistance were informed by previously published systematic reviews and meta-analyses.

TB Cascade Estimation Methods

We calculated national-level estimates for each step of the TB care cascade in Zambia in 2018 (**Table 1, Supplementary Appendix**). This included: Step 1: The total burden of active TB disease (individuals with prevalent TB in 2018); Step 2: the total number of individuals with TB who accessed TB testing; Step 3: the total number who were diagnosed with TB; Step 4: the total number who were notified and started on TB treatment; Step 5: the total number who successfully completed TB treatment. Each step of the cascade and the overall TB care cascade

were calculated among all patients and disaggregated according to rifampicin-resistance results (RR-TB and drug-susceptible TB [DS-TB]) and, among those with DS-TB, by HIV status. There was insufficient data available to characterize the RR-TB care cascade disaggregated according to HIV status. RR-TB was defined as the detection of rifampicin resistance on any clinical specimen using Xpert, molecular line probe assay or liquid culture; this definition therefore encompassed all patients with MDR-TB and extensively drug resistant TB (XDR-TB). DS-TB was defined as any TB case without known rifampicin resistance; thus, there is a possibility that patients with other forms of drug-resistance, including isoniazid monoresistance may have been included in this definition. However, unless rifampicin resistance is detected, TB drug susceptibility testing is not routinely performed in Zambia – this reflects the clinical reality of many high burden TB settings and conforms with WHO recommendations

The approach to all estimates followed recommendations outlined in a published set of methods for constructing national-level TB care cascades [6]. An overview of the approach used to calculate each step of the TB care cascade is summarized in **Table 1** and is described in brief below; however, a highly detailed summary of all assumptions, calculations, estimates, and data sources is summarized in the **Supplementary Appendix**.

We first started with Step 4 (the total number of patients who were notified and started on TB treatment - including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated individuals [30]) and Step 5 (the total number who successfully completed TB treatment), which were both directly informed by exact values from aggregated facility-level notification data. Step 3 (the total number who were diagnosed with TB) was then back calculated from the number of individuals notified (Step 4) and the proportion of patients who were estimated to have been lost-to-follow-up (LTFU) prior to initiation of TB therapy (pre-treatment LTFU), which was informed by aggregated facility-level laboratory data. Step 2 (the total number of individuals with TB who accessed TB testing) was calculated by adding the number of individuals with TB who would not have been microbiologically diagnosed due to the incomplete sensitivity of TB diagnostic tests (based upon published reports), corrected for the number of test-negative TB patients who were empirically diagnosed, to the number of total TB patients diagnosed (Step 3). The overall approach for Steps 2-5 was similar for both

DS-TB and RR-TB (**Table 1 and Supplementary Appendix**). The overall TB burden (all forms) was estimated using the WHO TB incidence estimate for 2018, plus 50% of the number all individuals with TB that remained undiagnosed in 2017; a 50% estimate has previously been utilized and assumed that the remaining 50% of undiagnosed individuals with TB in 2017 either self-cured or died [8,31]. To determine the total number of individuals with rifampicin resistant TB (Step 1), we multiplied the overall TB burden by the proportion of all patients who had rifampicin resistance detected during the Zambian national drug resistance survey [22]. The total number of individuals with DS-TB was calculated using the total TB burden minus the number of RR-TB cases.

All "gaps" between each step were calculated by taking the difference in the total number of individuals with TB and the uncertainty estimate (either 95% confidence intervals or range) between the succeeding and proceeding step. All TB care cascades were depicted graphically using bar charts representing the absolute number of cases and associated uncertainty measurement (if applicable). For each step of each cascade, proportions relative the total TB burden (Step 1) as well as relative to the prior step were calculated. It should be noted that several steps of the cascade utilized exact numbers from aggregated facility-level programmatic data (steps 3, 4, and 5); for the purposes of these analyses, data were assumed to be accurate and complete; however, such data may be incompletely recorded and a small proportion may be entered incorrectly - estimates of uncertainty around exact values from programmatic data were unavailable. Furthermore, unique patient identifiers are not available within Zambia's NTP and thus this analysis does not present a cohort of individuals that were tracked through each step of the TB care cascade; while we assumed for the purposes of this analysis that the same patients were being characterized at each step of the cascade, one cannot exclude the possibility that different individuals are being captured at different steps of the care cascade.

Evaluating Diagnostic and Treatment Outcomes

To understand any progress that may have underpinned the 2018 TB care cascade, we also evaluated TB diagnostic and treatment completion trends from 2015 to 2018. Using facility-level aggregated laboratory data, we plotted (a) the total number of sputum Xpert tests undertaken each year against the total number of pulmonary TB cases diagnosed each year, including the

proportion that was microbiologically confirmed as well as (b) the total number of Xpert tests undertaken (on any specimen) each year against the total number of RR-TB cases diagnosed and notified each year. We also plotted the proportion (and corresponding 95% confidence interval) of TB patients each year who started TB treatment that successfully completed it, disaggregated according to TB type: (1) new/relapse pulmonary TB – overall (2) HIV-positive new/relapse pulmonary TB, (3) HIV-negative new/relapse pulmonary TB, (4) retreatment TB not including individuals who experienced relapse, and (5) extra-pulmonary TB.

Results

Overall National TB Care Cascade for 2018

In 2018, the overall burden of TB in Zambia was estimated to comprise 72,495 individuals with TB (range, 40,495-111,495; **Table 2; Figure 1a**). Of the total burden of individuals with TB, 43,387 (range, 42,390-44,710; 59.8%) were estimated to have sought care for their TB illness and undergone microbiologic TB testing. Among these individuals 40,176 (range, 40,128-40,212; proportion of total TB burden - 55.4%) were diagnosed with TB, 36,431 (exact value; proportion of total TB burden – 50.3%) were notified and initiated on TB therapy and 32,700 (exact value; proportion of total TB burden – 45.1%) completed TB therapy. Therefore, 39,795 (range, 8,191-79,191; 54.9%) of the estimated individuals with TB in 2018 did not complete the care cascade (**Table 3**). Individuals who did not seek care for their TB illness or who sought care but did not undergo microbiological TB testing accounted for 29,108 (range, 0-66,777; 73.1%) individuals with TB lost along the cascade in 2018 (**Table 3)**; suboptimal empirical diagnosis of individuals with TB who had negative microbiological test results (due to incomplete diagnostic sensitivity of these tests) contributed to an additional 3,211 (95%CI, 2,262-4,506; 8.1%) missed TB cases, losses-to-follow-up prior to TB treatment initiation accounted for 3,745 (95%CI, 3,697-3,781; 9.4%) patients lost, and unfavorable outcomes (loss to follow-up, death, and treatment failure) prior to TB treatment completion accounted for 3,731 (exact value; 9.4%) patients lost.

TB Care Cascade by Drug Susceptibility Result

We estimated the burden of individuals with DS-TB in 2018 to be 70,755 (range, 40,009-107,481) - approximately 97.6% of the total TB burden. The DS-TB cascade was largely similar to the overall TB cascade with 32,304 (exact value; 45.7%) of all individuals being diagnosed with TB, initiating on and completing TB treatment (**Table 2; Figure 1b)**. The total number of RR-TB cases was estimated to be 1,740 (range, 486-4,014), or 2.4% of the total TB burden. Compared to individuals with DS-TB, individuals with RR-TB were substantially less likely to access microbiological TB testing (52.3% vs. 60.0%, p<0.001), have their TB diagnosed (68.9% vs. 93.1%, p<0.001), be notified and initiated on TB treatment (81.2% vs. 90.8%, p<0.001) and to complete TB therapy (77.8% vs. 89.9%, p<0.001) (**Figure 1c)**. Thus, only 396 (exact value; 22.1%) individuals with RR-TB completed the TB care cascade. The majority of those with RR-

TB along the pathways were due to individuals who did not seek care or who did not have access to TB and/or drug susceptibility testing – accounting for 830 cases (range, 0-2,961; 61.7%, **Table 3**); however, 283 (95%CI, 149-466; 21.1%) of lost RR-TB cases were among those who accessed TB testing and had RR-TB missed, 118 (exact value; 8.8%) were among those who had RR-TB detected but were not notified and started on appropriate TB therapy, and 113 (exact value; 8.4%) were among those who did not complete RR-TB therapy (**Table 3**).

Drug Susceptible TB Care Cascade by HIV status

Of 70,755 individuals with drug-susceptible TB in 2018, 43,411 (range, 23,911-65,911; 61.4%) were estimated to be among people living with HIV. Compared to patients with DS-TB who were HIV-negative, HIV-positive patients with DS-TB were less likely to access microbiological TB testing (57.0 vs. 64.8%, p<0.001) and were less likely to complete TB treatment (88.4% vs. 92.1%, p<0.001). This resulted in a lower overall proportion of HIV-positive patients compared to HIV-negative patients completing the TB care cascade (42.8% vs. 50.2%, p<0.001; **Table 2; Figures 1d and 1e**). For both HIV-positive and HIV-negative patients with DS-TB, the largest loss in the care cascade was due to patients not accessing microbiological TB testing resulting in 18,597 (range, 0-40,495; 75.2%) and 10,939 (range, 98-24,620; 70.6%) missed patients, respectively.

TB Diagnosis Trends from 2015 to 2018

Between 2015 and 2018 Xpert MTB/RIF was increasingly utilized as the first-line TB diagnostic tool in Zambia where 24,140 Xpert tests were sent for suspected pulmonary TB in 2015, which increased to 163,470 sent in 2018 (**Figure 2a**). During this same period, the number of sputum AFB smear microscopy investigations decreased from 95,300 in 2015 to 25,323 in 2018. While there was a small decrease in the absolute number of pulmonary TB cases diagnosed and notified in 2018 compared to 2015 (31,272 vs. 33,452), the proportion of microbiologically-confirmed TB cases that were notified during that period, substantially increased (56.0% [95CI, 55.5-56.6] vs. 44.1% [95%CI, 43.6-44.7]; **Figure 2a**). The scale-up of Xpert testing between 2015 and 2018 was also associated with a more than three-fold increase in the annual number of RR cases detected (627 vs. 196), and more than five-fold increase in the annual number of RR-TB cases that were notified and started on appropriate TB treatment (509 vs. 99; **Figure**

2b). During this period, there was a corresponding reduction in the proportion of RR-TB cases LTFU prior to the initiation of TB treatment from 49.5% in 2015 to 18.8% in 2018 (p<0.001).

TB Treatment Completion Trends from 2015 to 2018

Finally, we examined trends in the proportion of DS-TB patients who completed TB treatment once they were notified and initiated on therapy (**Figure 3**). Among new/relapse pulmonary TB cases, treatment completion rates steadily increased between 2015 and 2018 (86.2 [95%CI: 85.8-86.6] vs. 90.3% [95%CI: 90.0-90.7]; p<0.001). There was also a trend towards improved TB treatment completion rates from 2015 to 2018 among retreatment pulmonary TB cases (84.4% [95%CI: 83.3-85.5] vs. 87.2% [95%CI: 84.5-89.6]; p=0.06), however completion rates declined from 2017 to 2018 (95.0% [95%CI: 93.4-96.3] vs. 87.2% [95%CI: 84.5-89.6]; p<0.001). From 2015 to 2018, the proportion of patients with extrapulmonary TB completing TB treatment also improved (80.3% [95%CI: 79.4-81.1] vs. 87.8% [95%CI: 87.4-89.3]; p<0.001). The proportion of HIV-positive patients completing TB therapy did not meaningfully change from 2015 to 2018 (87.3% [95%CI: 86.9-87.7] vs. 88.4% [95%CI: 88.0-88.9]; p=0.001). Improvements in treatment completion rates from 2015 to 2018 were seen among patients who had a negative or unknown HIV status (82.4% [95%CI: 81.8-82.9] vs. 91.8% [95%CI: 91.4-92.2]; p<0.001) although, there was a small decline between 2017 and 2018 (93.7% [95%CI: 93.3-94.1] vs. 91.8% [95%CI:91.4-92.2]; p<0.001; **Figure 3**). In 2018, a lower proportion of HIV-positive TB patients completed therapy compared to HIV-negative patients (difference 3.4% [95%CI: 2.8-4.0]; p<0.001). Differences in the proportion of patients completing TB therapy according to HIV status were driven by a higher absolute number and proportion of cases that died or were LTFU during treatment among HIV-positive individuals compared to HIV-negative individuals (**Supplementary Table 1).**

Discussion

In this study we found that less than half of all TB cases in Zambia in 2018 were diagnosed with TB, initiated on TB treatment and completed therapy. We identified important losses at each step of the TB care cascade, however, we estimate that more than 40% of all individuals with TB in Zambia are not accessing microbiological TB testing – this accounted for nearly three-quarters of the estimated number of cases lost throughout the cascade. These results highlight

important research and programmatic priorities for improving TB care and TB-related outcomes in Zambia.

This represents the fourth national TB care cascade that has been characterized from a high burden TB country and builds upon similar analyses from South Africa, India, and Madagascar [7–9]. Our overall TB care cascade results are similar to those from these countries that each found that only about 50% of all TB patients were progressing through all steps of the care cascade and completing TB treatment. In India the largest losses in the care cascade were among those who did not access TB testing (28% of all cases) [7], in Madagascar the largest losses in the cascade were among those who were not diagnosed with TB despite seeking care and accessing a TB diagnostic facility (26% of all cases) [9], while in South Africa steady losses were seen prior to TB diagnosis (12% of all cases), prior to starting TB treatment (13% of all cases) and prior to successful completion of TB therapy (17% of all cases) [8]. In Zambia, 40% were estimated to have not accessed TB testing, while 4-5% of all TB cases were lost at each subsequent step of the care cascade. These differences highlight specific programmatic needs at different steps within the TB care cascade for each country and provides insight into the unique challenges that they each face.

Our results are consistent with several TB prevalence surveys suggesting that a large proportion of individuals with TB face barriers to healthcare seeking, barriers to accessing microbiological TB testing, or both [32,33]. Unfortunately, we are not able to discern whether the estimated 40% gap in patients not accessing TB microbiological investigations is predominantly driven by (a) individuals who fundamentally lacked access to primary health and TB facilities, (b) individuals who either delayed or never presented to TB testing facilities for evaluation of their illness, or (c) individuals who sought care at health facilities, but their illness was not suspected to be TB and thus they never had TB testing undertaken [34]. After onset of symptoms, individuals with undiagnosed TB may have long and complex journeys to TB care as they often face many barriers to care-seeking and accessing TB services (e.g., lack of knowledge, lack of social support, lack of time/finances, TB/HIV-related stigma, cultural and gender norms) [33,35,36]. In the last Zambian national TB prevalence survey conducted in 2013 and 2014, only 60% of previously undiagnosed individuals with TB were symptomatic, of whom 50% had sought care

for their illness at a health facility [12]. Furthermore, once patients do access healthcare services, their TB illness may be missed – this has been shown to be a common problem in recent standardized patient studies conducted in Kenya [37], India [38] , and China [39].

Collectively, this suggests that both community-based and facility-based active TB case finding strategies, as well as training of healthcare providers to improve recognition of and testing for TB, are likely to be important to activities to increase detection of individuals with TB in Zambia. Community-based active TB case finding may help overcome individuals' barriers to health-seeking and accessing TB services, possibly resulting in a greater absolute number of TB patients diagnosed and patients who are detected earlier [40–42]. However, effective and sustainable community-based active TB case finding strategies are not well-described and represent an urgent TB research need [33,43]. There is strong evidence demonstrating that facility-based, active TB case finding strategies are efficient and may yield a large number of cases that would otherwise have been missed, especially in high burden settings [44–47]. A recent study evaluating a multicomponent active TB case finding strategy in a high burden primary health care facility in Lusaka, Zambia found that total TB notifications increased by 35% during the intervention period; of the total TB cases, 91.5% were from facility-based case finding interventions while 8.5% were from community-based case finding interventions [47]. One important component of this strategy was the implementation of patient-friendly TB fast-track points at health facilities that improved access by allowing individuals with TB symptoms to skip the regular que and undergo rapid screening and testing for TB. Further research is needed to understand what potential strategies to improve TB care engagement and diagnosis are most preferred by and acceptable to community members in high-burden settings.

We estimate that nearly 10% of individuals diagnosed with TB were LTFU prior to the initiation of TB treatment. Pre-treatment LTFU is common in many high-burden settings as demonstrated by a systematic review that found that 4-38% (weighted proportion 18%) of TB patients in sub-Saharan Africa were lost at this step in the cascade [48]. This may be accounted for by patients who died prior to initiation of therapy – a common finding among such patients – and patients who cannot be traced after diagnosis either due to missing/incorrect contact information, or because they have moved away. A recent qualitative study among TB patients and health care

workers (HCW) in India provided further understanding of the factors that may contribute to LTFU prior to the initiation of TB therapy [49]. The authors identified challenges and constraints related to organizational and administrative barriers resulting in patient disengagement from TB services over frustration as well as negative HCW attitudes and behaviors resulting in patient distrust and feeling that their autonomy had been violated. There is an important need to design, evaluate and implement strategies that may address patient-level and health system factors and reduce pre-treatment LTFU [48]. It should be noted that pre-treatment loss-to-follow-up estimates may be overestimated because they fail to account for individuals who were in fact started on TB therapy but were not officially registered and therefore never notified to the NTP (under-notification). Zambia's NTP has recently completed a study to estimate the proportion of patients who are diagnosed but not notified as well as the proportion of those who are started on treatment but never reported. This study will yield improved estimates of pre-treatment loss-to-follow-up, which will allow for improved evaluations of programmatic changes that aim to improve TB diagnosis and linkage to TB treatment and care.

We found that important progress has been made in Zambia with regard to microbiological TB diagnosis and TB treatment completion from 2015 to 2018. During this period there was a massive effort to scale-up the availability of Xpert MTB/RIF as the first-line TB diagnostic for all forms of TB. This was associated with a 12% increase in the proportion of TB patients who were microbiologically-confirmed (2,692 additional annual drug-susceptibility patients). Importantly, because Xpert also provides rapid simultaneous detection of rifampicin-resistance, its scale-up was also associated with a three-fold increase in RR-TB patients detected and a five-fold increase in the number of RR-TB patients who were notified and started on TB treatment. Zambia is currently preparing to scale-up Xpert Ultra cartridges, which when paired with continued efforts to decentralize Xpert testing, should allow for further gains in the detection of HIV-associated TB, extra-pulmonary TB, and RR-TB [50]. There was also evidence of improved TB treatment completion rates for nearly all forms of TB between 2015 and 2018. While it is important to recognize progress that has been made, smaller but critically important gaps in the TB care cascade remain due to missed diagnoses and lack of treatment completion. Further efforts to expand access to microbiological TB testing and interventions to bolster TB treatment adherence that are grounded in person-centered care approaches - such as decentralization of

services coupled with improved education and communication as well as material and psychological support - are needed [51,52].

PLHIV accounted for 60% of DS-TB cases in Zambia and were more likely to be lost at several steps of the cascade compared to HIV-negative individuals. This finding emphasizes the need to strengthen HIV-TB collaborative activities [33,53]. Due to non-specific clinical presentations and radiographic findings, one of the most important challenges to improving HIV-associated TB outcomes remains TB diagnosis [54]. Non-specific symptoms may delay care-seeking among PLHIV, and without systematic TB screening among PLHIV presenting to and in-care, the diagnosis of many TB cases may be further delayed or missed. Systematic screening for TB at each clinical presentation [55] must be coupled with access to improved microbiological diagnostic tools such as Xpert Ultra [56] and urine LAM [56,57] testing to facilitate rapid TB detection and TB treatment initiation in order to minimize pre-treatment loss-to follow-up and improve clinical outcomes. Compared to HIV-negative patients, HIV-positive patients were less likely to complete TB therapy, and TB treatment completion rates among PLHIV did not significantly change over a four-year period from 2015 to 2018. Previously, a study among PLHIV in Zambia found that a large number of individuals LTFU from HIV services had died and that programmatic mortality rates were substantially under-reported [23]; this suggests that mortality among PLHIV LTFU from TB treatment services is high and that TB-related mortality among PLHIV in Zambia is likely underestimated. The implementation of tailored interventions to improve adherence to TB treatment [51,58] as well as antiretroviral therapy [59] among this highly vulnerable population therapy are needed.

Notably, we found that less than one quarter of RR-TB cases in 2018 were detected, started on appropriate treatment and completed appropriate therapy. This was despite improved access to rapid drug susceptibility via the scale-up of Xpert MTB/RIF testing from 2015 to 2018 and shorter and simplified drug-resistant TB regimens being introduced in 2018 [16]. The high rate of attrition of RR-TB patients throughout the care cascade argues for the need for specific investments in systems strengthening to improve drug resistant TB diagnosis and treatment in Zambia, mirroring this dire need in most high TB burden countries [19,33,60,61]. One important contributing factor to the large number of RR-TB patients not accessing DST is the high

proportion of patients who are being diagnosed clinically and/or on the basis of radiological findings only – this accounted for approximately 44% of pulmonary TB cases in Zambia in 2018. Notably, the scale-up of Xpert testing between 2015 to 2018 was associated with a more than 30% reduction in the proportion of RR-/MDR-TB cases that were LTFU after diagnosis and prior to initiation of treatment – this is likely due to the substantially faster detection of rifampicin resistance compared to conventional culture-based methods. Collectively, this demonstrates the importance of continued efforts to expand access to Xpert testing in Zambia in order to facilitate confirmation of TB diagnoses coupled with rapid detection of rifampicin resistance. While the implementation of existing diagnostic tools as well as improved DR-TB treatment regimens must be optimized, there remains a continued need for the development of rapid low-cost drug susceptibility testing (DST) that can be scaled-up to provide decentralized access to first- and second-line DST aligned with current treatment recommendations [62], as well as continued progress towards shorter, less toxic, and more effective DR-TB treatment regimens [63].

This study utilized a validated analysis method [6] incorporating a number of data sources to derive nationally representative estimates of the TB care cascade in Zambia; however, there were some limitations. As with other published TB cascades analyses, there is uncertainty around the estimates, especially the overall number of TB cases. The total burden of TB was calculated using indirect estimates from modelling that were based upon case notification data and a prior national TB prevalence survey. We derived a conservative estimate of the total TB burden that accounted for missed cases from the prior year [8] and that therefore may be a more appropriate estimate than measurements of TB incidence, which are rarely feasible to directly estimate [64]. Due to a lack of a unique national patient identifier, we were unable to link specific individuals with their outcomes as they progressed through the TB care cascade and thus unique individuals in one step of the cascade may differ from those in the following step; where possible, we attempted to account for duplicate diagnostic and treatment data, which was uncommon. Implementation of a unique TB patient identifier, and an improved TB data surveillance program with enhanced data integration would greatly improve future estimates and allow for real time individual-level, facility-level, and sub-national-level data to inform program strengthening.

Given the potential importance of gender to TB epidemiology [32,65] and potential differential health-seeking behaviors and access to TB services [36,66,67], we sought to characterize the TB care cascade among men and women. For example, the prevalence of TB among men in Zambia's first national TB prevalence survey in 2013/2014 was almost twice as high as that among women (833 vs. 487 cases per 100,000 persons) [12] and men with presumptive TB were less likely to have sought care for their symptoms than women (31.4% vs. 38.4%) [68]. Unfortunately, sex-disaggregated data sources were not available that would have allowed for each step of the cascade to be estimated. It is important that TB programs collect sex-disaggregated diagnostic and treatment data to help ensure equity in access and treatment benefits. Additionally, because core incidence, diagnosis, notification and treatment numbers are from 2018, we feel our analysis accurately represents the national TB care cascade in 2018; however, pre-treatment LTFU estimates were informed by patient-level data from 2017 and the proportion of cases with rifampicin resistance were informed by higher-end estimates from the most recent national drug resistance survey conducted in 2008 [22]. An updated drug resistance survey is currently underway and will provide new estimates that will better guide programmatic priorities. Finally, to our knowledge, there are no locally or regionally-representative estimates of TB relapse rates after documented TB treatment completion. This is an important quality metric of individuals' adherence to therapy as well as TB treatment programs and should be assessed in future research studies [6].

In conclusion, in 2018 only 45% of individuals with TB in Zambia completed the TB care cascade, and most losses were among patients who never accessed TB testing. Additionally, only 22% of all RR-TB patients successfully completed appropriate TB treatment and HIV-positive patients had substantially worse TB outcomes compared to HIV-negative patients. Our results suggest that continued systems-strengthening coupled with patient-centered engagement strategies are required throughout the TB cascade of care, however, implementation of active TB case finding strategies coupled with a renewed focus on those with rifampicin-resistance and PLHIV are urgently needed to improve TB-related outcomes and TB control in Zambia.

Contributions

PL, ADK and MM conceived the study. PL, RC, AS and KM were responsible for project administration. CCK, JM, and SN collected and organized the data. ADK conducted the analysis and developed the figures with input from PL, MM, RS, MK, CCK, JM, SN, RC, AS, and KM. ADK, PL, and MM wrote the first draft of the manuscript. All authors contributed to interpretation of data and editing of the article and approved the final version of the manuscript before submission.

Funding

ADK was supported by the National Institute of Allergy and Infectious Diseases (Grant No T32 AI060530).

Disclaimer

The funding sources had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the manuscript for publication.

Data availability statement

All data relevant to this study are included in the article or uploaded as supplementary information.

Competing Interests

All authors declare no competing interests.

References

1 World Health Organization. The End TB Strategy. World Health Organization, Geneva; 2015.
2 World Health Organization. Global Tuberculosis Report 2020. World Health Organization, Geneva; 2020.
3 Centers for Disease Control. CDC in Zambia. Center for Disease Control and Prevention, Atlanta; 2017.
4 Medland NA, McMahon JH, Chow EP, *et al.* The HIV care cascade: a systematic review of data sources, methodology and comparability. *J Int Aids Soc* 2015;**18**:20634. doi:10.7448/ias.18.1.20634
5 Reid MJA, Goosby E. Lessons learned from the HIV care cascade can help End TB. *Int J Tuberc Lung Dis* 2017;**21**:245–6. doi:10.5588/ijtld.17.0027
6 Subbaraman R, Nathavitharana RR, Mayer KH, *et al.* Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLOS Med* 2019;**16**:e1002754-18. doi:10.1371/journal.pmed.1002754
7 Subbaraman R, Nathavitharana RR, Satyanarayana S, *et al.* The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002149-38. doi:10.1371/journal.pmed.1002149
8 Naidoo P, Theron G, Rangaka MX, *et al.* The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. *J Infect Dis* 2017;**216**:S702–13. doi:10.1093/infdis/jix335
9 Knoblauch AM, Lapierre SG, Randriamanana D, *et al.* Multidrug-resistant tuberculosis surveillance and cascade of care in Madagascar: a five-year (2012–2017) retrospective study. *BMC Med* 2020;**18**:173. doi:10.1186/s12916-020-01626-6
10 United Nations Population Fund. Zambia - Overview. United Nations Population Fund, Geneva; 2020.
11 Joint United Nations Programme on HIV/AIDS. Country factsheets - Zambia 2019. Joint United Nations Programme on HIV/AIDS, Geneva; 2020.
12 Kapata N, Chanda-Kapata P, Ngosa W, *et al.* The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. *PLOS ONE* 2016;**11**:e0146392-14. doi:10.1371/journal.pone.0146392
13 Zambian Ministry of Health. Underreporting of TB patients in Zambia. National TB and Leprosy Programme, Lusaka; 2019.
14 The National Tuberculosis and Leprosy Program. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in Zambia. 2017.
15 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. World Health Organization, Geneva; 2017.
16 Challenge TB. Rapid Scale-Up of New Drugs and Regimens for the Treatment of Drug-Resistant TB in Zambia. FHI 360 Zambia Office, Lusaka 2020.
17 Zambia Ministry of Health. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection: 2018.
18 World Health Organization. Global Tuberculosis Report 2018. World Health Organization, Geneva; 2018.
19 World Health Organization. Global Tuberculosis Report 2019. World Health Organization, Geneva; 2019.

20 Glaziou P, Sismanidis C, Dodd PJ, Zignol M, Floyd K. Methods used by WHO to estimate the global burden of TB disease. World Health Organization, Geneva; 2018.

21 World Health Organization. Tuberculosis data. https://www.who.int/teams/global-tuberculosis-programme/data

22 Kapata N, Mbulo G, Cobelens F, *et al.* The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health* 2015;**20**:1492–500. doi:10.1111/tmi.12581

23 Holmes CB, Sikazwe I, Sikombe K, *et al.* Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. *PLOS Med* 2018;**15**:e1002489. doi:10.1371/journal.pmed.1002489

24 Zambia Statistics Agency, Ministry of Health (MOH) Zambia, and ICF. 2019. Zambia Demographic and Health Survey 2018. Lusaka, Zambia, and Rockville, Maryland, USA: Zambia Statistics Agency, Ministry of Health, and ICF.

25 Horne DJ, Kohli M, Zifodya JS, *et al.* Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2019 Jun; 2019(6): CD009593. doi: 10.1002/14651858.CD009593.pub4

26 Boehme CC, Nicol MP, Nabeta P, *et al.* Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *The Lancet* 2011;**377**:1495–505. doi:10.1016/s0140

27 Steingart KR, Henry M, Ng V, *et al.* Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006;**6**:570–81. doi:10.1016/s1473-3099(06)70578-3

28 World Health Organization. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. World Health Organization, Geneva; 2016.

29 Tortoli E, Benedetti M, Fontanelli A, *et al.* Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Micro* 2002;**40**:607–10. doi:10.1128/jcm.40.2.607-610.2002

30 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization, Genevea; 2014.

31 Dye C. Breaking the law: tuberculosis disobeys Styblo's rule. *Bull World Health Organ* 2008;**86**:4–4. doi:10.2471/blt.07.049510

32 Horton KC, MacPherson P, Houben RMGJ, *et al.* Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002119. doi:10.1371/journal.pmed.1002119

33 Reid MJA, Arinaminpathy N, Bloom A, *et al.* Building a tuberculosis-free world: The Lancet Commission on tuberculosis. *Lancet* 2019;**393**:1331–84. doi:10.1016/s0140-6736(19)30024-8

34 Subbaraman R, Jhaveri T, Nathavitharana RR. Closing gaps in the tuberculosis care cascade: an action-oriented research agenda. *J Clin Tuberc Other Mycobact Dis* 2020;**19**:100144. doi:10.1016/j.jctube.2020.100144

35 Vries SG de, Cremers AL, Heuvelings CC, *et al.* Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. *Lancet Infect Dis* 2017;**17**:e128–43. doi:10.1016/s1473-3099(16)30531-x

36 Krishnan L, Akande T, Shankar AV, *et al.* Gender-Related Barriers and Delays in Accessing Tuberculosis Diagnostic and Treatment Services: A Systematic Review of Qualitative Studies. *Tuberc Res Treat* 2014;**2014**:1–14. doi:10.1155/2014/215059

37 Daniels B, Dolinger A, Bedoya G, *et al.* Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. *BMJ Glob Health* 2017;**2**:e000333. doi:10.1136/bmjgh-2017-000333

38 Kwan A, Daniels B, Saria V, *et al.* Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. *PLOS Med* 2018;**15**:e1002653. doi:10.1371/journal.pmed.1002653

39 Sylvia S, Xue H, Zhou C, *et al.* Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. *PLOS Med* 2017;**14**:e1002405. doi:10.1371/journal.pmed.1002405

40 Kranzer K, Afnan-Holmes H, Tomlin K, *et al.* The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013;**17**:432–46. doi:10.5588/ijtld.12.0743

41 STOB TB Partnership. Finding the Missing People with TB in Communities. Stop TB Partnership, Geneva; 2018.

42 Marks GB, Nguyen NV, Nguyen PTB, *et al.* Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New Engl J Med* 2019;**381**:1347–57. doi:10.1056/nejmoa1902129

43 Kerkhoff AD, Muyoyeta M, Cattamanchi A. Community-wide Screening for Tuberculosis. *New Engl J Med* 2020;**382**:1185–6. doi:10.1056/nejmc1916666

44 Shapiro AE, Chakravorty R, Akande T, Lonnroth K, Golub JE. A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. World Health Organization, Geneva; 2013.

45 STOB TB Partnership. Intensified TB Case Finding at Facility Level. Stop TB Partnership, Geneva; 2018.

46 Hanrahan CF, Nonyane BAS, Mmolawa L, *et al.* Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). *PLOS Med* 2019;**16**:e1002796. doi:10.1371/journal.pmed.1002796

47 Kagujje M, Chilikutu L, Somwe P, *et al.* Active TB case finding in a high burden setting; comparison of community and facility-based strategies in Lusaka, Zambia. *PLOS ONE* 2020.

48 MacPherson P, Houben RM, Glynn JR, *et al.* Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bull World Health Organ* 2013;**92**:126–38. doi:10.2471/blt.13.124800

49 Thomas BE, Suresh C, Lavanya J, *et al.* Understanding pretreatment loss to follow-up of tuberculosis patients: an explanatory qualitative study in Chennai, India. *BMJ Glob Health* 2020;**5**:e001974. doi:10.1136/bmjgh-2019-001974

50 Dorman SE, Schumacher SG, Alland D, *et al.* Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis* 2018;**18**:76–84. doi:10.1016/s1473-3099(17)30691-6

51 Alipanah N, Jarlsberg L, Miller C, *et al.* Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLOS Med* 2018;**15**:e1002595. doi:10.1371/journal.pmed.1002595

52 World Health Organization. A patient-centered approach to TB care. World Health Organization, Geneva; 2018.

53 World Health Organization. WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders. World Health Organization, Geneva; 2012.

54 Kerkhoff AD, Cattamanchi A. Diagnosis of HIV-Associated Tuberculosis. In: Sereti I, Bisson GP, Meintjes G (eds) HIV and Tuberculosis: A Formidable Alliance. Springer, Cham. 2019; 127-159.

55 World Health Organization. WHO Consolidated Guidelines on Tuberculosis, Module 2: Systematic Screening for Tuberculosis Disease. World Health Organization, Geneva; 2021.

56 World Health Organization. WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. World Health Organization, Geneva; 2017.

57 World Health Organization. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019. World Health Organization, Geneva; 2019.

58 Subbaraman R, Mondesert L de, Musiimenta A, *et al.* Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *BMJ Glob Health.* 2018;**3**:e001018. doi:10.1136/bmjgh-2018-001018

59 Kanters S, Park JJH, Chan K, *et al.* Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017;**4**:e31–40. doi:10.1016/s2352-3018(16)30206-5

60 Dowdy DW, Theron G, Tornheim JA, *et al.* Drug-resistant tuberculosis in 2017: at a crossroads. *Lancet Respir Medicine* 2017;**5**:241–2. doi:10.1016/s2213-2600(17)30081-4

61 Dheda K, MD PTG, MMed PGM, *et al.* The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med.* 2017;**5**:291–360. doi:10.1016/s2213-2600(17)30079-6

62 World Health Organization. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. World Health Organization, Geneva; 2014.

63 Kendall EA, Sahu S, Pai M, *et al.* What will it take to eliminate drug-resistant tuberculosis? *Int J Tuberc Lung Dis* 2019;**23**:535–46. doi:10.5588/ijtld.18.0217

64 Stop TB Partnership. TB Impact Measurement. Stop TB Partnership, Geneva; 2012.

65 Horton KC, Sumner T, Houben RMGJ, *et al.* A Bayesian Approach to Understanding Sex Differences in Tuberculosis Disease Burden. *Am J Epidemiol* 2018;**187**:2431–8. doi:10.1093/aje/kwy131

66 Chikovore J, Hart G, Kumwenda M, *et al.* 'For a mere cough, men must just chew Conjex, gain strength, and continue working': the provider construction and tuberculosis care-seeking implications in Blantyre, Malawi. *Glob Health Action* 2015;**8**:26292. doi:10.3402/gha.v8.26292

67 Chikovore J, Hart G, Kumwenda M, *et al.* TB and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. *Int J Tuberc Lung Dis* 2017;**21**:26–33. doi:10.5588/ijtld.16.0925

68 Chanda-Kapata P, Kapata N, Masiye F, *et al.* Health Seeking Behaviour among Individuals with Presumptive Tuberculosis in Zambia. *PLOS ONE* 2016;**11**:e0163975-11. doi:10.1371/journal.pone.0163975

Figure Legend

Figure 1. The tuberculosis care cascade in Zambia in 2018 among: (a) all tuberculosis cases; (b) drug-susceptible cases; (c) rifampicin-resistant cases; (d) drug-susceptible cases among HIV-positive individuals; (e) drug-susceptible cases among HIV-negative individuals**.**

Figure 2. Diagnoses and notifications of (a) all forms of drug-susceptible pulmonary tuberculosis in Zambia between 2015 and 2018, and (b) drug-resistant tuberculosis in Zambia between 2015 and 2018.

Figure 3. Overview of drug-susceptible tuberculosis treatment outcomes in Zambia between 2015 and 2018, disaggregated according to tuberculosis-type. Shapes represent the proportion of patients completing tuberculosis treatment.

Supporting information

Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV status.

Table 1. Approach to and data sources for estimating each step of the tuberculosis care cascade in Zambia in 2018.

	Step 1. TB burden	Step 2. Accessed tests	Step 3. Diagnosed	Step 4. Notified and treated	Step 5. Successfully treated
All TB cases	WHO estimates of TB incidence in 2018 plus 50% of the number of undetected cases from 2017 [19,21].	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV status (informed by published reports [25–27]), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual level data from 4 Zambian provinces in 2017).	Back calculated from number of cases notified (step 4) and proportion of patients lost-to-follow-up (LTFU) prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 [unpublished]) and number of microbiologically confirmed DS PTB cases notified (informed by aggregated facility-level TB notification data from 2018 [unpublished]).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Add DS-TB and RR-TB cases successfully treated.
Rifampicin-resistant TB cases	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance (informed by most recent Zambia National TB drug resistance survey in 2008 [22]).	Back calculated from RR-TB cases diagnosed (step 3) on the basis of cases bacteriologically diagnosed, by test type and test sensitivity (informed by published reports [25,28,29]).	Exact value from aggregated facility-level TB laboratory data from 2018 (unpublished).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases, all cases	Overall TB burden minus RR-TB cases.	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV status (informed by published reports [25–27]), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual level data from 4 Zambian provinces in 2017).	Back calculated from number of DS-TB cases notified (step 4) and proportion of LTFU prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 [unpublished]) and number of microbiologically confirmed DS PTB cases notified (informed by aggregated facility-level TB notification data from 2018 [unpublished]).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases,	WHO 2019 analysis of DS-TB incidence in 2017 plus 50% of the number of undetected	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB	Back calculated from number of cases notified (step 4) and proportion of patients LTFU prior to initiation of TB therapy (pre-	Exact value from aggregated facility-level TB notification data from 2018	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (number successfully treated)

HIV-positive individuals	cases from 2018 [19,21].	cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated ([25,26]).	treatment LTFU assumed to be the same independent of HIV status).	adjusted for the proportion of patients without an HIV test. (unpublished).	adjusted for proportion of patients without an HIV test (unpublished).
Drug-susceptible TB cases, HIV-negative individuals	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals.	Total number of DS-TB cases who accessed TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals.	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals.	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified.	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated.

Table 2. Overview of the tuberculosis care cascade in Zambia in 2018 according to type.

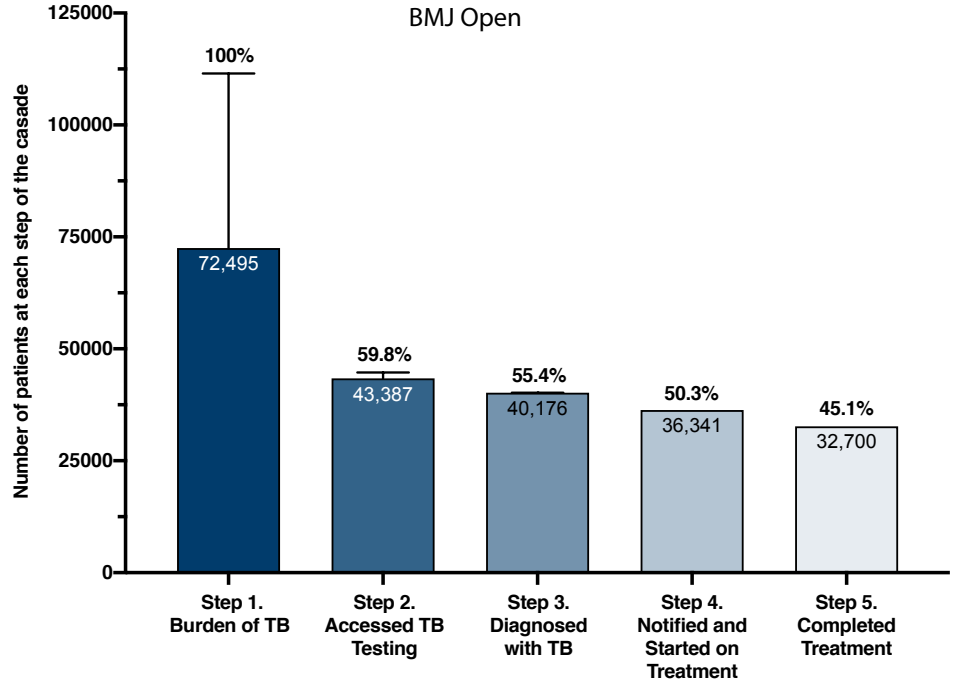
	Step 1. TB burden		Step 2. Accessed tests			Step 3. Diagnosed			Step 4. Notified and treated			Step 5. Successfully treated		
	Cases, range*	% of total burden^	Cases, range*	% of total burden^	% relative to prior step#	Cases, range*	% of total burden^	% relative to prior step#	Cases, range*	% of total burden^	% relative to prior step#	Cases, range*	% of total burden^	% relative to prior step#
Overall TB Cascade	72,495 (40,495-111,495)	100	43,387 (95%CI: 42,390-44,710)	59.8	59.8	40,176 (95%CI: 40,128-40,212)	55.4	92.6	36,431	50.2	90.7	32,700	45.1	89.8
Rifampin-resistant TB	1,740 (486-4,014)	100	910 (95%CI: 776-1,093)	52.3	52.3	627	36.0	68.9	509	29.3	81.2	396	22.8	77.8
Drug-susceptible TB, all	70,755 (40,009-107,481)	100	42,477 (95%CI: 41,614-43,625)	60.0	60.0	39,549 (95%CI: 39,501-39,585)	55.9	93.1	35,922	50.8	90.8	32,304	45.7	89.9
HIV-positive, drug-susceptible TB	43,411 (23,911-65,911)	100	24,746 (95%CI: 24,290-25,349)	57.0	57.0	23,133 (95%CI: 23,106-23,154)	53.3	93.5	21,012 (95%CI: 20,962-21,064)	48.4	90.8	18,579 (95%CI: 18,535-18,625)	42.8	88.4
HIV-negative, drug-susceptible TB	27,344 (16,098-41,570)	100	17,731 (95%CI: 17,324-18,276)	64.8	64.8	16,415 (95%CI: 16,395-16,431)	60.0	92.6	14,910 (95%CI: 14,858-14,960)	54.5	90.8	13,725 (95%CI: 13,679-13,769)	50.2	92.1

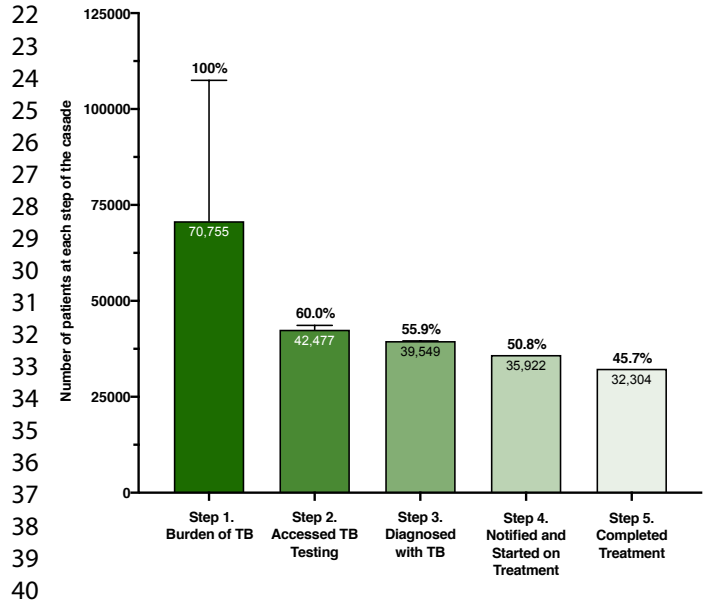
*Values in parentheses represent ranges, unless explicitly specified as 95% confidence intervals. ^Value represents the proportion of TB cases relative to the total TB burden (Step 1). #Value represents the proportion of TB cases relative to the prior step in the cascade.

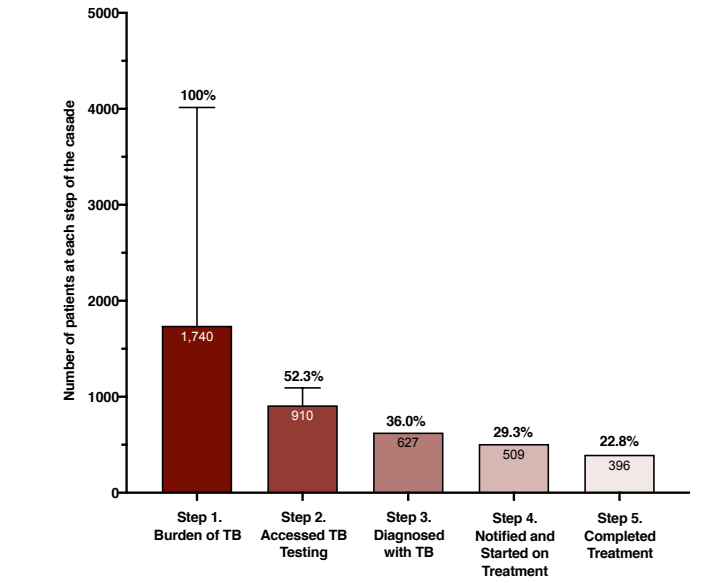
Table 3. Gap analysis of the tuberculosis care cascade in Zambia in 2018 according to type.

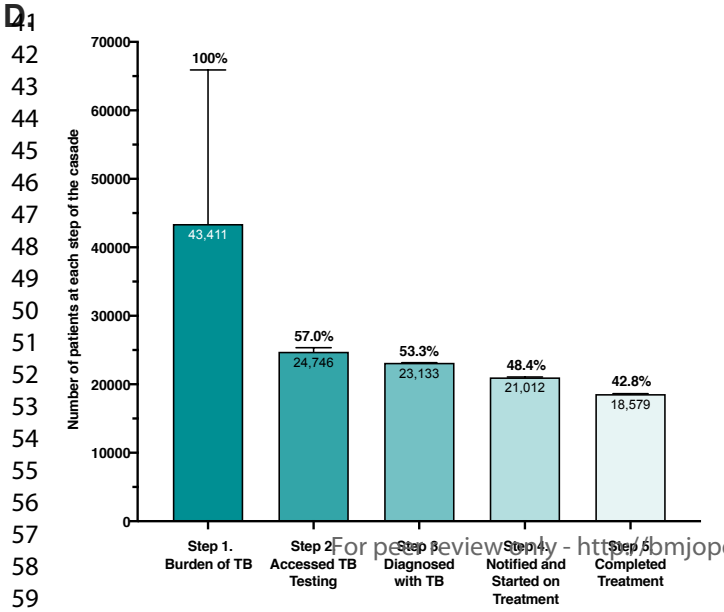
	Overall TB cases lost throughout the care cascade		Gap 1. Patient did not seek care at TB facility and/or have TB tests sent		Gap 2. TB tests sent, but TB missed		Gap 3. TB diagnosed but patient not started on TB treatment and/or not notified		Gap 4. TB treatment started, but not completed	
	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^
Overall TB Cascade	39,795 (8,191-79,191)	100	29,108 (0-66,777)	73.1	3,211 (95%CI: 2,262-4,506)	8.1	3,745 (95%CI: 3,697-3,781)	9.4	3,731	9.4
Rifampin-resistant TB	1,344 (486-4,014)	100	830 (0-2,921)	61.7	283# (95%CI: 149-466)	21.1	118	8.8	113	8.4
Drug-susceptible TB, all	38,451 (40,009-107,481)	100	28,278 (0-63,856)	73.5	2,928 (95%CI: 2,112-4,040)	7.6	3,627 (95%CI: 3,579-3,663)	9.4	3,618	9.4
HIV-positive, drug-susceptible TB	24,832 (5,376-47,286)	100	18,597 (0-40,495)	75.2	1,613 (95%CI: 1,185-2,194)	6.5	2,121 (95%CI: 2,094-2,142)	8.5	2,379 (95%CI: 2,337-2,529)	9.8
HIV-negative, drug-susceptible TB	13,619 (2,419-27,801)	100	10,939 (98-24,620)	70.6	1,315 (95%CI: 927-1,846)	9.7	1,505 (95%CI: 1,486-1,520)	11.1	1,239 (95%CI: 1,089-1,281)	8.7

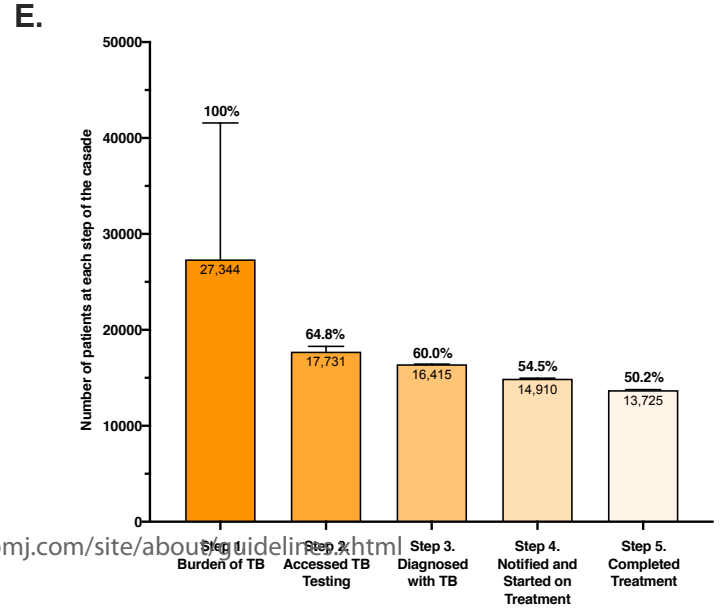
*Values in parentheses represent ranges, unless explicitly specified as 95% confidence intervals. ^Proportions are relative to the total number of TB cases estimated to have been lost throughout the care cascade. #For rifampicin resistant TB, either the TB diagnosis or the rifampicin resistance was missed.



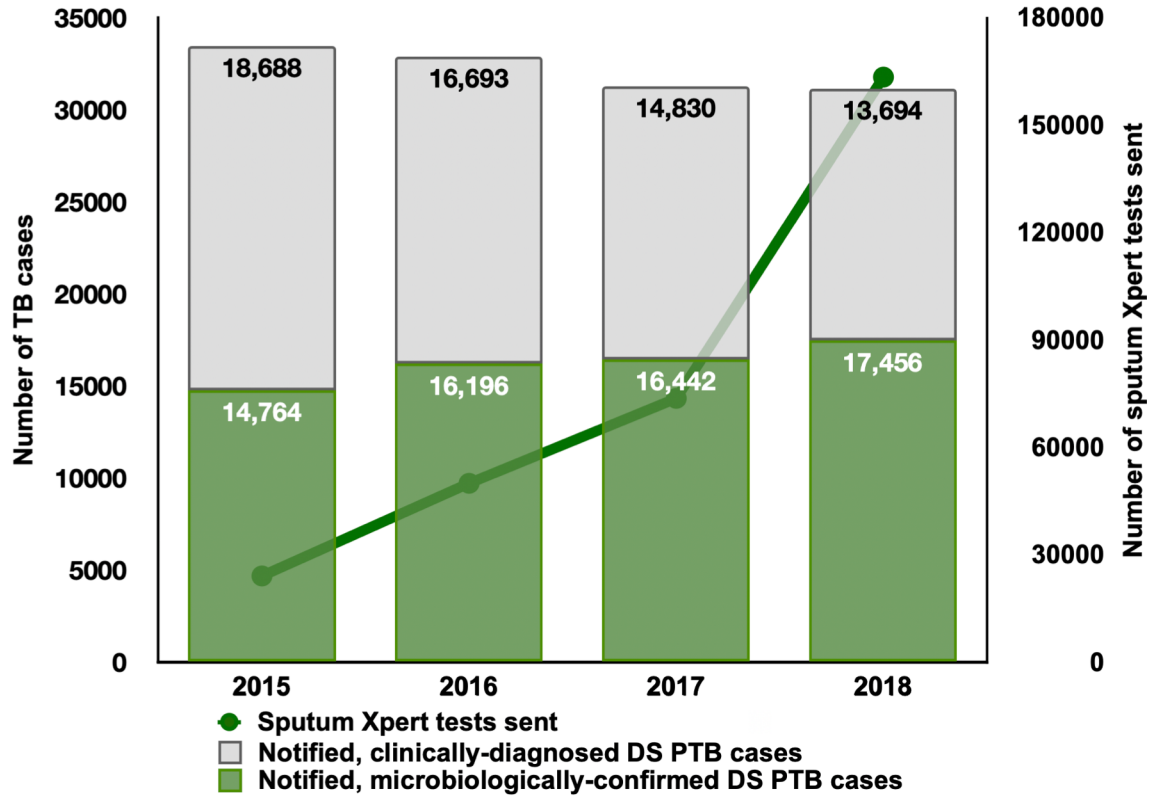




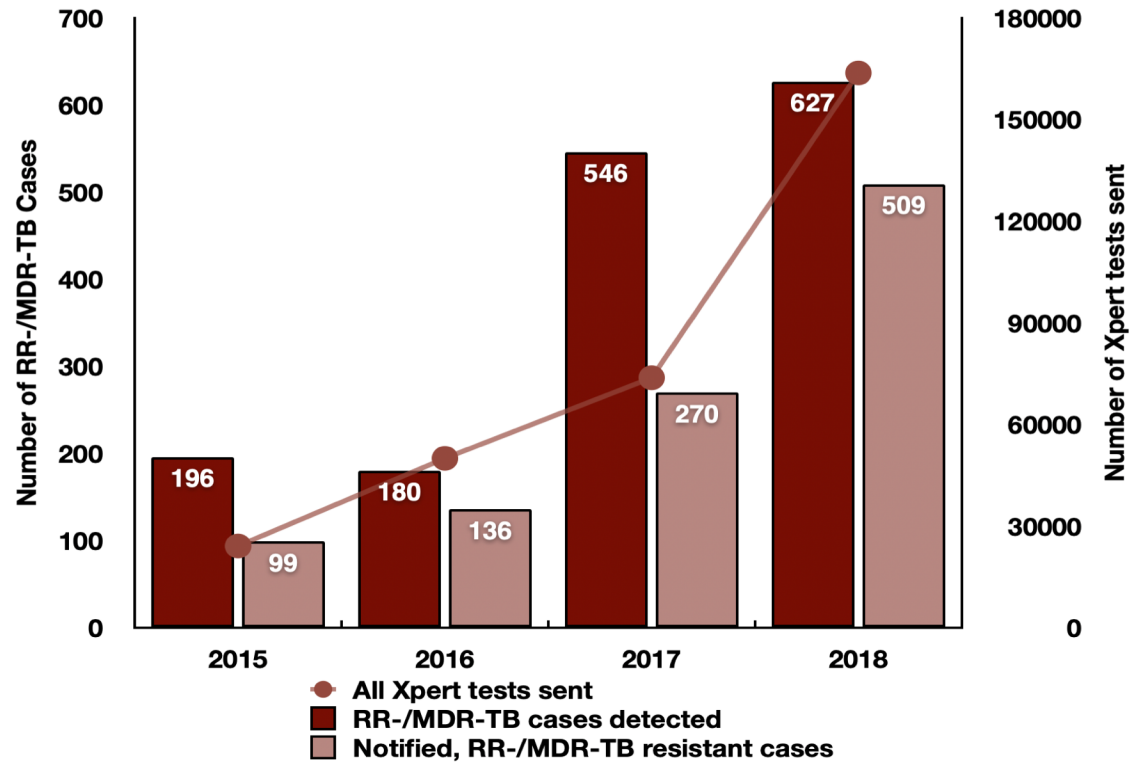


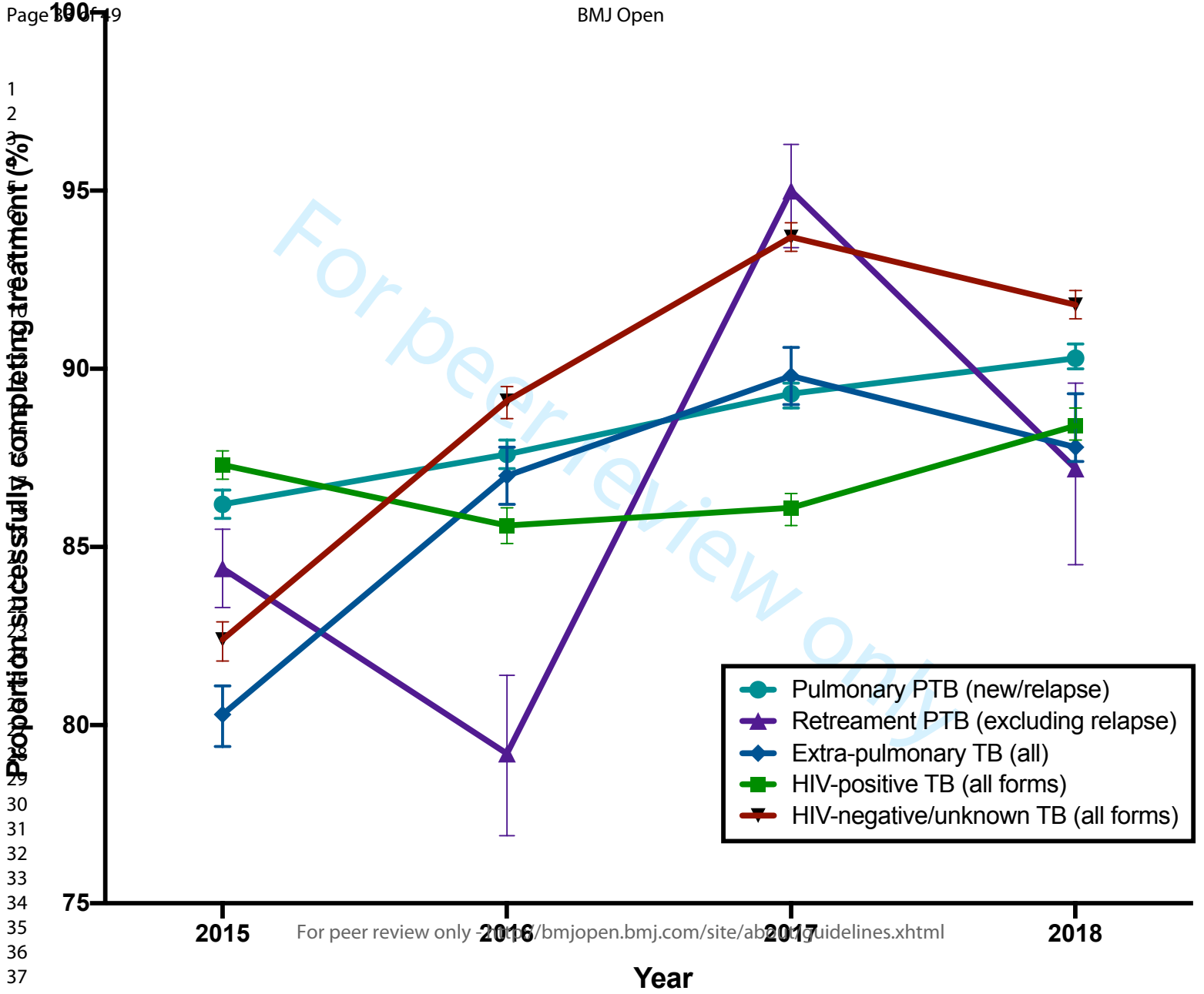


A.


35000
30000
25000
20000
15000
10000
5000
0
Number of TB cases
180000
150000
120000
90000
60000
30000
0
Number of sputum Xpert tests sent
18,688
16,693
14,830
13,694
14,764
16,196
16,442
17,456
2015
2016
2017
2018
Sputum Xpert tests sent
Notified, clinically-diagnosed DS PTB cases
Notified, microbiologically-confirmed DS PTB cases

B.


700
600
500
400
300
200
100
0
Number of RR-/MDR-TB Cases
180000
150000
120000
90000
60000
30000
0
Number of Xpert tests sent
196
99
180
136
546
270
627
509
2015
2016
2017
2018
All Xpert tests sent
RR-/MDR-TB cases detected
Notified, RR-/MDR-TB resistant cases



Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Table 1. Overall TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. TB burden	72,495 (40,495 - 111,495)	100	WHO 2019 analysis of TB incidence in 2018 plus 50% of the number of undetected cases from 2017.[1]	• TB incidence, 2018 (all): 60,000 • TB incidence, 2017 (all): 61,000 • Case detection rate, 2017: 59.0% • Estimated undetected cases 2017: 24,990 • 50% of undetected cases who have not died/self-cured: 12,495
Gap 1	29,108 (0-66,777)	40.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	43,387 (95%CI: 42,390-44,718)	59.8	Add DS-TB and RR-TB cases that accessed TB testing (see Tables 2 and 3 for estimates).	• DS-TB: 42,477 (95%CI: 41,614-43,625) • RR-TB: 910 (95%CI: 776-1,093)
Gap 2	3,211 (95%CI: 2,262-4,506)	4.4	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed	40,176 (95%CI: 40,128-40,212)	55.4	Add DS-TB and RR cases diagnosed (see Tables 2 and 3 for estimates).	• DS-TB: 39,549 (95%CI: 39,501-39,585) • RR-TB: 627
Gap 3	3,745 (95%CI: 3,697-3,781)	5.2	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated	36,431	50.2	Add DS-TB and RR cases notified and treated (see Tables 2 and 3 for estimates).	• DS-TB: 35,922 • RR-TB: 509
Gap 4	3,731	5.1	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated	32,700	45.1	Add DS-TB and RR cases successfully treated (see Tables 2 and 3 for estimates).	• DS-TB: 32,304 • RR-TB: 396

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 2a. Drug-susceptible TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	70,755 (40,009-107481)	100	Overall TB burden minus RR-TB cases.	• TB burden: 72,495 (40,495-111,495) • RR cases: 1740 (486-4014)
Gap 1	28,278 (0-63,856)	40.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	42,477 (95%CI: 41,614-43,625)	60.0	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV-status, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 39,549 (95%CI: 39,501-39,585) • Number missed: 2,928 (95%CI: 2,112-4,040)
Gap 2	2,928 (95%CI: 2,112-4,040)	4.1	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	39,549 (95%CI: 39,501-39,585)	55.9	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS PTB cases detected and number of microbiologically confirmed DS PTB cases notified (Table 2c).	• Pre-treatment LTFU estimate: = 9.2 (95%CI: 9.1-9.3) • Number of patients notified in 2018: 35,922
Gap 3	3,627 (95%CI: 3,579-3,663)	5.1	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	35,922	50.8	Exact value from aggregated facility-level TB notification data.	• All patients with DS-TB who were notified and started on treatment (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).
Gap 4	3,618	5.1	Step 4 estimated cases minus Step 5 estimated cases	
Step 5. Successfully treated for TB.	32,304	45.7	Exact value from aggregated facility-level TB treatment outcomes data.	• All patients with DS-TB who successfully completed TB therapy (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).

Table 2b. Estimation method for determining number of patients with DS-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall
Total number of all microbiologically-confirmed TB cases (who therefore underwent microbiological tests)[1]	8,025 (PTB) + 320 (EPTB) = 8,345	9,803 (PTB)+1,137 (EPTB) = 10,940	19,285
Number of the above who underwent Xpert[1]	7,320	9,071	16,391
Number who underwent smear[1]	1,025	1,869	2,894
Proportion who underwent smear only (were smear-positive but Xpert either not done, or negative)[2]	96.9% (95%CI: 95.6-98.0)	98.1% (95%CI: 97.1-98.8)	97.7% (95%CI:96.9-98.3)
Number who underwent smear only	1,025 x .969% (95%CI: .956-.980) = 993 (95%CI: 980-1,005)	1,869 x .981% (95%CI: .971-.988) = 1,833 (95%CI: 1815-1,847)	-
Sensitivity of Xpert[3]	81% (95%CI 75-86)	88% (95%CI: 83-92)	85% (95%CI: 82-88)
Cases missed by Xpert	7,320/ .81 (95%CI .75-.86) - 7,320 = 1,717 (95CI: 1,192-2,440)	9,071 /.88 (95%CI: .83-.92)- 9,071 = 1,237 (95%CI: 789-1,858)	2,594 (95%CI: 1,980-4,298)
Sensitivity of smear microscopy[4,5]	50% (95%CI:42-57)	76% (95%CI: 70-80)	-
Cases missed by smear	993/0.50 (95%CI:0.42-0.57)- 993 = 1,025 (95%CI: 773-1,415)	1,833/0.76 (0.70-0.80)-1,833 = 590 (95%CI: 467-801)	1,615 (95%CI: 1,240-2,216)
Total combined cases missed by Xpert and smear	2,472 (95CI: 1,965-3,855)	1,827 (95%CI: 1,256-2,659)	4,569 (95%CI: 3,221-6,514)
Proportion of patients who had a negative Xpert that were empirically treated[2]	30.6% (95%CI: 28.6-32.7)	22.7% (95%CI:19.8-25.9)	28.9 (95%CI: 27.2-30.6)
Negative Xpert / received empiric therapy	1,717 (95CI: 1,192-2,440) x .306 (95%CI: .286-.327) = 525 (95: 341-798)	1,237 (95%CI: 789-1,858) x .227 (95%CI:.198-259) = 281 (95%CI: 156-481)	806 (95%CI: 497-1,279)

Proportion of patients who had a negative smear that were empirically treated[2]	58.9% (95%CI: 56.8-61.0)	39.2% (95%CI: 36.9-41.4)	50.1 (95%CI 48.5-51.6)
Negative smear / received empiric therapy	1,025 (95%CI: 773-1,415) x .589 (95%CI: .568-.610) = 604 (95%CI: 439-863)	590 (95%CI: 467-801) x .392% (95%CI: .369-.414) = 231 (95%CI: 172-332)	835 (95%CI: 612-1,195)
Total cases that were negative by Xpert or smear that were empirically treated	1,129 (95%CI: 780-1,661)	529 (95%CI: 329-813)	1,641 (95%CI: 1,109-2,474)
Total Missed cases (Total number of cases missed by Xpert or smear minus those were empirically treated)	1,613 (95%CI: 1,185-2,194)	1,315 (95%CI: 927-1,8460	2,928 (95%CI: 2,112-4,040)

[1]Exact value from 2018 national TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished), [3]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593.[4]Estimate from: Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 377:1495–505. [5]Estimate from: Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:570–81.

Table 2c. Estimation method for determining proportion of patients with pre-treatment lost-to-follow-up.

Variable	Overall
Unadjusted number of microbiologically-confirmed pulmonary TB cases[1]	19,285 (16,391 Xpert and 2,894 smear)
Proportion of patients with positive smear who also have a positive Xpert result[2]	2.3% (95%CI 1.7-3.1)
Number of patients with positive smear who also have a positive Xpert result[2]	2,894 x .023% (95%CI .017-.031) = 67 (95%CI: 49-90)
Adjusted number of microbiologically-confirmed PTB cases	(2,894 - 67 (95%CI: 49-90)) + 19,218 (95%CI: 19,195-19,236)
Number of patients with microbiologically-confirmed pulmonary TB notified in 2018[3]	17,456
Proportion of all patients with microbiologically-confirmed TB who were registered and started TB treatment	90.8 (95%CI: 90.7-90.9)
Pre-treatment lost-to-follow-up (LTFU) estimate:	100% - 90.8 (95%CI: 90.7-90.9) = 9.2% (95%CI: 9.1-9.3)

[1]Exact value from 2018 nationally aggregated TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished).[3]Exact value from 2018 nationally aggregated TB notification register.

Table 3. Rifampicin resistant TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	1,740 (486-4,014)	100	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance.	• TB burden: 72,495 (40,495-111,495) • Overall estimate of RR-TB: 2.4% (95CI: 1.2-3.6)[1]
Gap 1	830 (range, 0-2,921)	47.7	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	910 (95%CI: 776-1,093)	52.3	Back calculated from RR tuberculosis cases diagnosed on the basis of cases bacteriologically diagnosed, by test type and test sensitivity.	• RR-TB cases diagnosed: 627 • RR-TB cases missed: 283
Gap 2	283 (95%CI: 149-466)	16.3	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	627	36.0	Exact value from aggregated facility-level TB laboratory data.	• All patients with microbiologically-confirmed RR-TB
Gap 3	118	6.8	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	509	29.3	Exact value from aggregated facility-level TB notification data.	• All patients with RR-TB who were notified and started on treatment.
Gap 4	113	6.5	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	396	22.8	Exact value from aggregated facility-level TB treatment outcomes data.	• The number of RR-TB who were notified and started on treatment who were successfully treated.

[1]Estimate from: Kapata N, Mbulo G, Cobelens F, et al. The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health*. 2015;20(11):1492-1500. This is the most recent Zambia national drug resistance survey. A higher estimate utilizing MDR-TB Plus chosen because it more closely coincides with WHO RR-TB incidence estimates for 2018.

Table 3b. Estimation method for determining number of patients with RR-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall, No
Number of laboratory-confirmed RR-cases	-	-	627
Proportion of RR-TB patients notified in 2018, by HIV-status.[1]	59.1% (95CI: 54.6-63.6)	40.9% (95%CI: 36.4-45.4)	-
Number of RR-TB patients diagnosed in 2018, by HIV-status	627 x 59.1% (95CI: 54.6-63.6) = 371 (95%CI: 342-399)	627 x 40.9% (95%CI: 36.4-45.4) = 256 (95%CI: 228-285)	627
Number of RR-cases detected by Xpert	-	-	372
Number of RR-cases detected by Xpert, by HIV-status	372 x 59.1% (95CI: 54.6-63.6) = 220 (95%CI: 203-237)	372 x 40.9% (95%CI: 36.4-45.4) = 152 (95%CI: 135-169)	372
Combined sensitivity of Xpert for Rif-Resistance, by HIV status[2]	• Sensitivity of Xpert for TB: 81% (95%CI: 75% to 86%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RR-TB: 77.8% (95%CI 70.5-83.4)	• Sensitivity of Xpert for TB: 88% (95%CI: 83% to 92%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RIF-resist TB: 84.5% (95%CI 78.0-89.2)	-
RR-cases missed by Xpert	220 (95%CI: 203-237)/ .778 (95%CI .705-.834) – 220 = 63 (95%CI: 24-116)	152 (95%CI: 135-169)/ .845 (95%CI .780-.892) – 152 = 28 (95%CI: 0-64)	91 (95%CI: 23-180)
Number of RR-cases detected by MDR-TB plus	-	-	135
Number of RR-cases detected by MDR-TB plus, by HIV-status	135 x 59.1% (95CI: 54.6-63.6) = 80 (95%CI: 74-86)	135 x 40.9% (95%CI: 36.4-45.4 = 55 (95%CI: 49-61)	135
Combined sensitivity of MDR-TB plus*[3]	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 48.5% (95%CI: 40.1-55.9)	• Sensitivity of smear for TB: 76% (95%CI: 70-80) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 73.6% (95%CI: 66.9-78.4)	-
RR-cases missed by MDR-TB plus	80 (95%CI: 74-86) /.485 (95%CI: .401-.559) - 80 = 85 (95%CI: 52-134)	55 (95%CI: 49-61) / .736 (95%CI: .669-.784) - 55 = 20 (95%CI: 7-36)	105 (95%CI: 59-171)

Number of RR-cases detected by liquid culture (MGIT 960)*[4]			120
Number of RR-cases detected by liquid culture (MGIT 960)*[4], by HIV-status	120 x 59.1% (95CI: 54.6-63.6) = 71 (95%CI: 66-76)	120 x 40.9% (95%CI: 36.4-45.4 = 49 (95%CI: 44-54)	120
Combined sensitivity of liquid culture	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 49.6% (40.3-57.0)	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 75.4 (95%CI: 67.1-80.0)	-
RR-cases missed by liquid culture	71 (95%CI: 66-76) / .496 (95%CI: .403-.570) – 71 = 72 (95%CI: 61-83)	43 (95%CI: 49-54) / .754 (95%CI: .671-.800) – 43 = 16 (95%CI: 6-32)	88 (95%CI: 67-115)
Total microbiologically-missed cases	63 (95%CI: 24-116) + 85 (95%CI: 52-134) + 72 (95%CI: 61-83) = 220 (95%CI: 137-333)	28 (95%CI: 0-64) + 20 (95%CI: 7-36) + 16 (95%CI: 6-32) = 64 (95%CI: 13-133)	283 (95%CI: 149-466)
Received empiric therapy*	0	0	0
Total Missed cases	220 (95%CI: 137-333)	64 (95%CI: 13-133)	283 (95%CI: 149-466)

[1]Exact value from 2018 national TB laboratory register. [2]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593. [3]Estimate from: WHO. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Geneva: WHO; 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1, [4]Estimated from: Tortoli E, Benedetti M, Fontanelli A, Simonetti MT. Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Microbiol*. 2002;40(2):607-610.

Table 4. Drug-susceptible TB Care Cascade among HIV-positive individuals in Zambia in 2018

Variable	Cases, range	Proportion (%), range	Estimation method	Calculation
Step 1. Overall TB burden	43,411 (23,911-65,911)	100	WHO 2019 analysis of TB incidence in 2017 plus 50% of the number of undetected cases from 2018.[1]	• TB incidence, 2018 (all): 36,000 (range, 23,000-51,000) • TB incidence, 2017 (all): 36,000 (range, 23,000-51,000) • Case detection rate, 2017: 58.8% (range, 41.5-92.1) • Estimated undetected cases 2017: 14,822 (range, 1,822-29,822) • 50% of undetected cases who have not died/self-cured: 7,411 (range, 911-14,911)
Gap 1	18,597 (0-40,495)	43.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	24,746 (95%CI: 24,290-25,349)	57.0	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 23,133 (95CI: 23,106-23,154) • Number missed (table 2b): 1,613 (95%CI: 1,185-2,194)
Gap 2	1,613 (95%CI: 1,185-2,194)	3.7	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	23,133 (95%CI: 23,106-23,154)	53.3	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy [see Table 2c]; [assumed to be the same independent of HIV-status].	• Pre-treatment LTFU estimate: 9.2% (95%CI: 9.1-9.3) • Number of HIV-positive patients notified in 2018: 21,012 (95%CI: 20,962-21,064)
Gap 3	2,121 (95%CI: 2,094-2,142)	4.9	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	21,012 (95%CI: 20,962-21,064)	48.4	Exact value from aggregated facility-level TB notification data adjusted for proportion of patients without an HIV test.	• DS-TB: 19,332 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

Gap 4	2,433 (95%CI: 2,337-2,529)	5.6	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	18,579 (95%CI: 18,535-18,625)	42.8	Exact value from aggregated facility-level TB treatment outcomes data (number successfully treated) adjusted for proportion of patients without an HIV test.	• DS-TB: 17,624 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 5. Drug-susceptible TB Care Cascade among HIV-negative individuals in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	27,344 (16,098-41,570)	100	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals	• Number of DS-TB cases: 70,755 (range, 40,009-107,481) • Number of HIV-positive DS-TB cases: 43,411 (23,911-65,911)
Gap 1	10,939 (98-24,620)	35.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	17,731 (95%CI: 17,324-18,276)	64.8	Total number of DS-TB cases who accesses TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals	• Number of DS-TB cases that accessed tests: 42,477 (95%CI: 41,614-43,625) • Number of HIV-positive DS-TB cases diagnosed: 24,746 (95%CI: 24,290-25,349)
Gap 2	1,315 (95%CI: 927-1,846)	4.8	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	16,415 (95%CI: 16,395-16,431)	60.0	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals	• Number of DS-TB cases diagnosed: 39,549 (95%CI: 39,501-39,585) • Number of HIV-positive DS-TB cases diagnosed: 23,133 (95%CI: 23,106-23,154)
Gap 3	1,505 (95%CI: 1,486-1,520)	5.5	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	14,910 (95%CI: 14,858-14,960)	54.5	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified	• Number of DS-TB cases notified: 35,922 • Number of HIV-positive DS-TB cases notified: 21,012 (95%CI: 20,962-21,064)
Gap 4	1,185 (95%CI: 1,089-1,281)	4.3	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	13,725 (95%CI: 13,679-13,769)	50.2	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated	• Number of DS-TB cases treated: 32,304 • Number of HIV-positive DS-TB cases treated: 18,633 (95%CI: 18,535-18,725)

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV-status.

	HIV-positive						HIV-negative or unknown HIV status					
	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated
2015	20967	18312 (87.3)	71 (0.3)	1117 (5.3)	682 (3.3)	785 (3.7)	20621	16986 (82.4)	102 (0.5)	1392 (6.8)	1168 (5.7)	973 (4.7)
2016	21655	18541 (85.6)	171 (0.8)	1354 (6.3)	705 (3.3)	884 (4.1)	18498	16481 (89.1)	55 (0.3)	1058 (5.7)	486 (2.6)	418 (2.3)
2017	20362	17527 (86.1)	136 (0.7)	1622 (8.0)	731 (3.6)	346 (1.7)	16841	15779 (93.7)	40 (0.2)	569 (3.4)	135 (0.8)	318 (1.9)
2018	19932	17624 (88.4)	113 (0.6)	1253 (6.3)	521 (2.6)	421 (2.1)	15990	14680 (91.8)	46 (0.3)	745 (4.7)	342 (2.1)	177 (1.1)

	Item No	Recommendation	Response:
Title and abstract			
	1	a) Indicate the study's design with a commonly used term in the title or the abstract	The design is included in the study title – **"The tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis." [p1]**
		b) Provide in the abstract an informative and balanced summary of what was done and what was found	This is provided (***see abstract [p2].***
Introduction			
Background	2	Explain the scientific background and rationale for the investigation being reported	This is described in the background section (see ***Background section paragraphs 2 and 3 [p4]).***
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific objectives are stated in the background section (see ***Background section paragraph 3 [p4]).***
Methods			
Study design	4	Present key elements of study design early in the paper	This is provided (***see Methods Section, paragraph 1 [p5]).***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up and data collection	This is provided (***see Methods Section, Setting and TB cascade data sources sub-sections [p5-7]).***
Participants	6	a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	This is provided (***see Methods Section, paragraph 1 [p5], and TB cascade data sources sub-section[p5-6]***)
		b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria if applicable	Outcomes, potential confounders and effect modifiers are described in detail (***see Methods Section, TB cascade estimation methods sub-section [p7-8]).***

Data sources/ measurements	8	For each variable of interest, give sources of data and details of methods of assessment. Describe comparability of assessment methods if there is more than one group	All data sources and methods of obtainment for variables of interest are described in detail (***see Methods Section, TB cascade estimation methods sub-section [p7-8], Table 1 and the Supplementary Appendix).***
Bias	9	Describe any efforts to address potential sources of bias	There are a few potential sources of bias that we discuss. One is the use of routine medical records, which may be incompletely documented. A second is that this analysis does not represent a cohort of individuals followed through each step of the care cascade; thus, different individuals may be captured at each step of the cascade. We also acknowledge that there is uncertainty around estimates (especially, TB incidence and incidence of rifampicin-resistance TB). These are discussed in detail (see ***Methods Section, TB cascade data sources sub-section [p6-7] and Discussion – paragraphs 9 and 10 [p18-19]).***
Study size	10	Explain how the study size was arrived at	We sought to include all persons with TB living in Zambia in 2018 (overall TB burden). We provide detailed information regarding how the total TB burden was calculated (***TB cascade estimation methods sub-section [p7-9]).***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	The analysis approach for all estimates is clearly detailed (***see Methods Section, TB cascade estimation methods sub-section [p7-9], Table 1 and the Supplementary Appendix).***
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	These details are provided in the methods section (***see Methods Section, TB cascade estimation methods sub-section, Table 1 and the Supplementary Appendix).***
		(b) Describe any methods used to examine subgroups and interactions	These details are provided in the methods section (***see Methods Section, TB cascade estimation methods sub-section [p7-9], Table 1 and the Supplementary Appendix).***
		(c) Explain how missing data were addressed	For the purposes of this analysis, data was assumed to be accurate and complete. This is described in the methods section (***see Methods Section, paragraph 1, and TB cascade data sources sub-section [p9]*).**
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable; estimating the number and proportion of patients lost-to-follow-up between each step of the TB care cascade was central to the study design (***see Methods Section, TB cascade estimation methods sub-section p7-9], Table 1 and the Supplementary Appendix and also Table 3).***
		(e) Describe any sensitivity analyses	No sensitivity analyses were conducted.
Results			

Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This information is described in results section (***See Results section [p11], Table 2 and Figure 1).***
		(b) Give reasons for non-participation at each stage	Not directly applicable. The number of individuals reaching each step of the cascade and that are lost throughout the cascade are characterized in detail (***See Results section [p11-12], Tables 2 and 3).***
		(c) Consider use of a flow diagram	Not directly applicable. The TB care cascade summarizing the number of individuals reaching step of the care cascade is characterized in detail (***See Results section [p11-12], Figure 1).***
Descriptive Data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	This information is provided in the results section (***See Results section [p11-12], Table 2)***
		(b) Indicate number of participants with missing data for each variable of interest	This does not apply. All data were assumed to be accurate and complete (***see 12c above***).
		(c) Summarise follow-up time (eg, average and total amount)	This does not apply.
Outcome data	15	Report numbers of outcome events or summary measures over time	For the main analysis, summary measures are restricted to a single year (2018) and are summarized in the results section (***See Results section [p11-12], Table 2 and Figure 1).*** For TB diagnostic and treatment outcomes between 2015 and 2018 these are also summarized in the results section ***(See Results section, sub-sections TB Diagnosis Trends from 2015 to 2018 [p12-13] and TB Treatment Completion Trends from 2015 to 2018 [p13] and as well as corresponding Figures 2 and 3).***
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	All analyses presented are unadjusted. Estimates were determined both overall and disaggregated by HIV status and TB drug-susceptibility status (***See Results section [p11-13], Tables 1-3 and Figures 1-3).***
		(b) Report category boundaries when continuous variables were categorized	This does not apply as no continuous variable were categorized.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	This does not apply.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	We present all analyses (including disaggregated analyses) (***see results section [p11-13]).***
Discussion			

Key Results	18	Summarise key results with reference to study objectives	Our discussion section summarizes key results with reference to the study objectives defined in the final paragraph of the background section (***see Discussion Section [p13-19]***).
	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	We provide a discussion on limitations and potential sources of bias ***(see Discussion Section, paragraphs 9 and 10 [p18-19]).***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	We have attempted to provide a conservative interpretation of our study results in the Discussion section and where appropriate linked our results to other published studies ***(see Discussion Section [p13-19])***
Generalisability	21	Discuss the generalisability (external validity) of the study results	This is described ***(see Discussion Section, paragraph 10 [p18-19]).***
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	This is described (***see section Funding section [p20]).***

BMJ Open

The tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-044867.R3
Article Type:	Original research
Date Submitted by the Author:	03-Jul-2021
Complete List of Authors:	Lungu, Patrick; Zambia Ministry of Health, National Tuberculosis and Leprosy Control Programme; University of Zambia University Teaching Hospital, Department of Internal Medicine Kerkhoff, Andrew; Zuckerberg San Francisco General Hospital and Trauma Center, Division of HIV, Infectious Diseases and Global Medicine Kasapo, Clara; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Mzyece, Judith; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Nyimbili, Sulani; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Chimzizi, Rhehab; National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia Silumesi, Andrew; Zambia Ministry of Health Kagujje, Mary; Center for Infectious Disease Research in Zambia Subbaraman, Ramnath; Tufts University School of Medicine, Department of Public Health and Community Medicine Muyoyeta, Monde ; Center for Infectious Disease Research in Zambia Malama, Kennedy; Ministry of Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Global health, Health services research
Keywords:	Tuberculosis < INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis

Short title: TB Care Cascade in Zambia

AUTHORS: Patrick S. Lungu[1,2*], Andrew D. Kerkhoff[3*], Clara C. Kasapo[1], Judith Mzyece[1], Sulani Nyimbili[1], Rhehab Chimzizi[1], Andrew Silumesi[4], Mary Kagujje[5], Ramnath Subbaraman[6], Monde Muyoyeta[5], Kennedy Malama[4]

Affiliations:

[1]National Tuberculosis and Leprosy Control Programme, Lusaka, Zambia
[2]Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia
[3]Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco, San Francisco, CA, USA
[4]Ministry of Health, Lusaka, Zambia
[5]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia
[6]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

*PSL and ADK contributed equally.

Corresponding author:
Dr. Patrick S. Lungu
Email: patrickpj456@yahoo.co.uk

Article type: Original article

Word Count: 5,717

Keywords: Tuberculosis, care cascade, loss to follow-up, Zambia, HIV, rifampicin resistance

Abstract

Objectives: Tuberculosis (TB) remains a leading cause of morbidity and mortality in Zambia, especially for people living with HIV (PLHIV). We undertook a care cascade analysis to quantify gaps in care and align program improvement measures with areas of need.

Design: Retrospective population-based analysis.

Setting: We derived national-level estimates for each step of the TB care cascade in Zambia. Estimates were informed by WHO incidence estimates, nationally aggregated laboratory and notification registers, and individual-level program data from four provinces.

Participants: All individuals with active TB disease in Zambia in 2018. We characterized the overall TB cascade and disaggregated by drug-susceptibility results and HIV status.

Results: In 2018, the total burden of TB in Zambia was estimated to be 72,495 (range, 40,495-111,495) cases. Of these, 43,387 (59.8%) accessed TB testing, 40,176 (55.4%) were diagnosed with TB, 36,431 (50.3%) were started on treatment and 32,700 (45.1%) completed treatment. Among all persons with TB lost at any step along the care cascade (n=39,795), 29,108 (73.1%) were lost prior to accessing diagnostic services, 3,211 (8.1%) prior to diagnosis, 3,745 (9.4%) prior to initiating treatment, and 3,731 (9.4%) prior to treatment completion. PLHIV were less likely than HIV-negative individuals to successfully complete the care cascade (42.8% vs. 50.2%; p<0.001). Among those with rifampicin-resistant TB, there was substantial attrition at each step of the cascade and only 22.8% were estimated to have successfully completed treatment.

Conclusions: Losses throughout the care cascade resulted in a large proportion of individuals with TB not completing treatment. Ongoing health systems strengthening, and patient-centered engagement strategies are needed at every step of the care cascade; however, scale-up of active case finding strategies is particularly critical to ensure individuals with TB in the population reach initial stages of care. Additionally, a renewed focus on PLHIV and individuals with drug-resistant TB is urgently needed to improve TB-related outcomes in Zambia.

Strengths and limitations of this study

- The national tuberculosis (TB) care cascade for Zambia in 2018 was characterized in order to identify gaps in care.
- The TB care cascade was constructed for all TB patients as well as according to drug-susceptibility result and HIV status.
- The analysis was informed by a published set of methodologies and utilized several data sources to derive estimates.
- Enhanced TB surveillance programs, including the use of unique TB patient identifiers, would allow for real-time monitoring and improved estimates to inform programmatic strengthening.

Background

The WHO End TB strategy aims to reduce tuberculosis (TB) incidence by 90% and TB-related deaths by 95% between 2015 and 2035 [1]. While many high burden countries in sub-Saharan Africa, including Zambia, have demonstrated large reductions in new TB cases and associated mortality, there remains significant need for improved TB care delivery [2]. TB remains a leading cause of morbidity and mortality in Zambia, especially among people living with HIV (PLHIV) [2,3]. In 2019, there were approximately 59,000 new individuals with active TB disease in Zambia (incidence rate of 333 per 100,000 per year) that resulted in 15,400 TB-related deaths, of which 62% were among PLHIV [2]. Despite substantial declines in TB incidence over the last decade, Zambia still has the seventh highest TB incidence in sub-Saharan Africa and remains one of 30 WHO high TB burden priority countries [2].

The HIV "cascade of care" is a public health model that outlines the key engagement steps required for PLHIV to ultimately achieve an undetectable viral load. This model has been widely applied by HIV programs globally to inform and strengthen HIV care and delivery and ultimately, significantly increase the number of PLHIV who know their HIV status, are started on ART and have suppressed viral loads [4]. Similarly, a national TB care cascade can provide key insights to identify and quantify gaps in the diagnosis and care of TB patients that could then help guide programmatic and research priorities by aligning limited resources with the areas of greatest need [5,6]. However, to-date, only three high burden TB countries - South Africa, India, and Madagascar - have undertaken and published national-level TB care cascade analyses [7–9].

We sought to construct a national TB cascade of care for Zambia to evaluate care delivery for individuals with active TB disease through enumeration of gaps in the overall care cascade in 2018 as well as disaggregated by rifampicin susceptibility results and HIV status. Estimates were derived using multiple data sources and the overall approach was informed by a recently published methodology for constructing TB care cascades [6].

Methods

Study design

We undertook a retrospective, population-based study to characterize the TB care cascade in Zambia in 2018. All Zambians estimated to be living with TB in 2018 were included in the analysis, regardless of age, HIV status, diagnosis status (i.e., diagnosed or undiagnosed TB), TB drug susceptibility status, or TB-type (i.e., new or retreatment).

Setting

Zambia has an estimated population of 18,400,000 people [10]. It has a high prevalence of HIV (11.5% among adults aged 15-49 years old), and it is estimated that at least 1.2 million persons are living with HIV [11]. TB is a major public health problem in Zambia [3]; during the last national TB prevalence survey conducted in 2013 and 2014, the prevalence of microbiologically-confirmed TB was estimated to be 638 per 100,000 persons and was five-times higher among HIV-positive individuals compared to HIV-negative individuals [12].

Testing and treatment for TB is almost universally provided within Zambia's public health system. While exact estimates are not available, likely <1% of all individuals with TB are detected and managed within Zambia's private sector and the large majority are reported to Zambia's National TB Program (NTP) – this assumption is informed by a national data quality audit conducted in 2019 [13].Within the public health sector, the direct costs of all TB diagnostics and treatment are provided free of charge. In 2018, Xpert MTB/RIF was the recommended first-line diagnostic for all individuals undergoing evaluation for possible TB (pulmonary or extra-pulmonary) in Zambia as well as initial drug-susceptibility testing (DST) [14]; however, it was not universally available at all facilities, in which case routine TB investigations included acid fast bacilli (AFB) fluorescence or Ziehl-Neelsen microscopy and chest radiography, where available. Among those with confirmed rifampicin-resistant (RR) or multidrug-resistant (MDR) TB, it was recommended that either liquid culture or a molecular line probe assay should be used as follow-on tests for further DST [14]. First line TB treatment was provided to all patients without evidence of rifampicin-resistance and consisted of isoniazid, rifampicin, ethambutol and pyrazinamide for

6-9 months in conformity with WHO recommendations [15]. In 2018, Zambia began scaling up shorter treatment regimens comprised of new and repurposed TB drugs for 9-12 months for eligible RR- and MDR-TB patients – this accounted for the majority of patients [16,17]; however, some patients still received longer MDR-TB treatment regimens comprised of several TB drugs, including an injectable agent, for at least 20 months.

In Zambia, patients diagnosed with TB are notified in a paper-based register and initiated on TB therapy at the corresponding TB treatment facility, which is also responsible for documentation of the treatment outcome of the patient. Data on diagnostic outcomes (laboratory register), notifications and treatment outcomes (notification register) are aggregated from each facility through the district office to the provincial level and then the national level on a monthly basis.

TB Cascade Data Sources

Several data sources were used to inform estimates within each of the five steps of the care cascade (**Table 1, Supplementary Appendix**). To inform estimates of the overall burden of TB in Zambia in 2018 (Step 1), WHO estimates of TB incidence from 2018 and 2017 were utilized [18–21]**.** The proportion of total individuals with TB estimated to be rifampicin-resistant was derived using estimates from the most recent national survey of TB drug resistance in Zambia [22]; this source was chosen in order to ground estimates of RR-TB in empiric data, however, higher-end estimates from the latest Zambian national survey of TB drug resistance in 2008 were used to more closely align with WHO incidence estimates for RR-TB in 2018. Diagnostic outcomes (Steps 2 and 3) were informed by a nationally aggregated database of TB diagnostics from 2018, which includes the number and type of investigations (Xpert or smear microscopy) and the number of TB patients detected according to type of TB investigation and HIV status. All treatment outcomes (Steps 4 and 5) were informed by a nationally aggregated TB treatment register from 2018.

Individual level programmatic data from four Zambian Provinces (Eastern, Lusaka, Southern, Western) regarding all patients investigated for TB and those started on treatment between January 1st and December 31st 2017 (n=43,896, n=11,814, respectively) was used to determine: (a) the proportion of patients who had both positive Xpert and smear microscopy results as well

as (b) the proportion of patients who were Xpert or smear-negative, but received empirical TB therapy. This helped to further refine estimates for Steps 2 and 3 by accounting for and removing duplicate patients (**Supplementary Appendix**). Patient-level data was only available from 4 out of 10 provinces; however, they account for nearly 60% of Zambia's national TB notifications and the range of socioeconomic characteristics of individuals as well as their access to healthcare services are representative of the other 6 provinces [23,24]. Unfortunately, robust data from 2018 to inform these estimates were unavailable – thus, we utilized 2017 data because it was well-characterized and temporally close to the year for which we sought to characterize the TB care cascade.

Diagnostic sensitivity estimates of Xpert [25] and smear microscopy [26,27] for the detection of TB stratified according to HIV status, as well as Xpert [25], molecular line probe assays [28] and liquid culture [29] for rifampicin-resistance were informed by previously published systematic reviews and meta-analyses.

TB Cascade Estimation Methods

We calculated national-level estimates for each step of the TB care cascade in Zambia in 2018 (**Table 1, Supplementary Appendix**). This included: Step 1: The total burden of active TB disease (individuals with prevalent TB in 2018); Step 2: the total number of individuals with TB who accessed TB testing; Step 3: the total number who were diagnosed with TB; Step 4: the total number who were notified and started on TB treatment; Step 5: the total number who successfully completed TB treatment. Each step of the cascade and the overall TB care cascade were calculated among all patients and disaggregated according to rifampicin-resistance results (RR-TB and drug-susceptible TB [DS-TB]) and, among those with DS-TB, by HIV status. There was insufficient data available to characterize the RR-TB care cascade disaggregated according to HIV status. RR-TB was defined as the detection of rifampicin resistance on any clinical specimen using Xpert, molecular line probe assay or liquid culture; this definition therefore encompassed all patients with MDR-TB and extensively drug resistant TB (XDR-TB). DS-TB was defined as any TB case without known rifampicin resistance; thus, there is a possibility that patients with other forms of drug-resistance, including isoniazid monoresistance may have been included in this definition. However, unless rifampicin resistance is detected, TB drug

susceptibility testing is not routinely performed in Zambia – this reflects the clinical reality of many high burden TB settings and conforms with WHO recommendations

The approach to all estimates followed recommendations outlined in a published set of methods for constructing national-level TB care cascades [6]. An overview of the approach used to calculate each step of the TB care cascade is summarized in **Table 1** and is described in brief below; however, a highly detailed summary of all assumptions, calculations, estimates, and data sources is summarized in the **Supplementary Appendix**.

We first started with Step 4 (the total number of patients who were notified and started on TB treatment - including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated individuals [30]) and Step 5 (the total number who successfully completed TB treatment), which were both directly informed by exact values from aggregated facility-level notification data. Step 3 (the total number who were diagnosed with TB) was then back calculated from the number of individuals notified (Step 4) and the proportion of patients who were estimated to have been lost-to-follow-up (LTFU) prior to initiation of TB therapy (pre-treatment LTFU), which was informed by aggregated facility-level laboratory data. Step 2 (the total number of individuals with TB who accessed TB testing) was calculated by adding the number of individuals with TB who would not have been microbiologically diagnosed due to the incomplete sensitivity of TB diagnostic tests (based upon published reports), corrected for the number of test-negative TB patients who were empirically diagnosed, to the number of total TB patients diagnosed (Step 3). The overall approach for Steps 2-5 was similar for both DS-TB and RR-TB (**Table 1 and Supplementary Appendix**). The overall TB burden (all forms) was estimated using the WHO TB incidence estimate for 2018, plus 50% of the number all individuals with TB that remained undiagnosed in 2017; a 50% estimate has previously been utilized and assumed that the remaining 50% of undiagnosed individuals with TB in 2017 either self-cured or died [8,31]. To determine the total number of individuals with rifampicin resistant TB (Step 1), we multiplied the overall TB burden by the proportion of all patients who had rifampicin resistance detected during the Zambian national drug resistance survey [22]. The total number of individuals with DS-TB was calculated using the total TB burden minus the number of RR-TB cases.

All "gaps" between each step were calculated by taking the difference in the total number of individuals with TB and the uncertainty estimate (either 95% confidence intervals or range) between the succeeding and proceeding step. All TB care cascades were depicted graphically using bar charts representing the absolute number of cases and associated uncertainty measurement (if applicable). For each step of each cascade, proportions relative the total TB burden (Step 1) as well as relative to the prior step were calculated. It should be noted that several steps of the cascade utilized exact numbers from aggregated facility-level programmatic data (steps 3, 4, and 5); for the purposes of these analyses, data were assumed to be accurate and complete; however, such data may be incompletely recorded and a small proportion may be entered incorrectly - estimates of uncertainty around exact values from programmatic data were unavailable. Furthermore, unique patient identifiers are not available within Zambia's NTP and thus this analysis does not present a cohort of individuals that were tracked through each step of the TB care cascade; while we assumed for the purposes of this analysis that the same patients were being characterized at each step of the cascade, one cannot exclude the possibility that different individuals are being captured at different steps of the care cascade.

Evaluating Diagnostic and Treatment Outcomes

To understand any progress that may have underpinned the 2018 TB care cascade, we also evaluated TB diagnostic and treatment completion trends from 2015 to 2018. Using facility-level aggregated laboratory data, we plotted (a) the total number of sputum Xpert tests undertaken each year against the total number of pulmonary TB cases diagnosed each year, including the proportion that was microbiologically confirmed as well as (b) the total number of Xpert tests undertaken (on any specimen) each year against the total number of RR-TB cases diagnosed and notified each year. We also plotted the proportion (and corresponding 95% confidence interval) of TB patients each year who started TB treatment that successfully completed it, disaggregated according to TB type: (1) new/relapse pulmonary TB – overall (2) HIV-positive new/relapse pulmonary TB, (3) HIV-negative new/relapse pulmonary TB, (4) retreatment TB not including individuals who experienced relapse, and (5) extra-pulmonary TB.

Results

Overall National TB Care Cascade for 2018

In 2018, the overall burden of TB in Zambia was estimated to comprise 72,495 individuals with TB (range, 40,495-111,495; **Table 2; Figure 1a**). Of the total burden of individuals with TB, 43,387 (range, 42,390-44,710; 59.8%) were estimated to have sought care for their TB illness and undergone microbiologic TB testing. Among these individuals 40,176 (range, 40,128-40,212; proportion of total TB burden - 55.4%) were diagnosed with TB, 36,431 (exact value; proportion of total TB burden – 50.3%) were notified and initiated on TB therapy and 32,700 (exact value; proportion of total TB burden – 45.1%) completed TB therapy. Therefore, 39,795 (range, 8,191-79,191; 54.9%) of the estimated individuals with TB in 2018 did not complete the care cascade (**Table 3**). Individuals who did not seek care for their TB illness or who sought care but did not undergo microbiological TB testing accounted for 29,108 (range, 0-66,777; 73.1%) individuals with TB lost along the cascade in 2018 (**Table 3)**; suboptimal empirical diagnosis of individuals with TB who had negative microbiological test results (due to incomplete diagnostic sensitivity of these tests) contributed to an additional 3,211 (95%CI, 2,262-4,506; 8.1%) missed TB cases, losses-to-follow-up prior to TB treatment initiation accounted for 3,745 (95%CI, 3,697-3,781; 9.4%) patients lost, and unfavorable outcomes (loss to follow-up, death, and treatment failure) prior to TB treatment completion accounted for 3,731 (exact value; 9.4%) patients lost.

TB Care Cascade by Drug Susceptibility Result

We estimated the burden of individuals with DS-TB in 2018 to be 70,755 (range, 40,009-107,481) - approximately 97.6% of the total TB burden. The DS-TB cascade was largely similar to the overall TB cascade with 32,304 (exact value; 45.7%) of all individuals being diagnosed with TB, initiating on and completing TB treatment (**Table 2; Figure 1b)**. The total number of RR-TB cases was estimated to be 1,740 (range, 486-4,014), or 2.4% of the total TB burden. Compared to individuals with DS-TB, individuals with RR-TB were substantially less likely to access microbiological TB testing (52.3% vs. 60.0%, p<0.001), have their TB diagnosed (68.9% vs. 93.1%, p<0.001), be notified and initiated on TB treatment (81.2% vs. 90.8%, p<0.001) and to complete TB therapy (77.8% vs. 89.9%, p<0.001) (**Figure 1c)**. Thus, only 396 (exact value; 22.1%) individuals with RR-TB completed the TB care cascade. The majority of those with RR-

TB along the pathways were due to individuals who did not seek care or who did not have access to TB and/or drug susceptibility testing – accounting for 830 cases (range, 0-2,961; 61.7%, **Table 3**); however, 283 (95%CI, 149-466; 21.1%) of lost RR-TB cases were among those who accessed TB testing and had RR-TB missed, 118 (exact value; 8.8%) were among those who had RR-TB detected but were not notified and started on appropriate TB therapy, and 113 (exact value; 8.4%) were among those who did not complete RR-TB therapy (**Table 3**).

Drug Susceptible TB Care Cascade by HIV status

Of 70,755 individuals with drug-susceptible TB in 2018, 43,411 (range, 23,911-65,911; 61.4%) were estimated to be among people living with HIV. Compared to patients with DS-TB who were HIV-negative, HIV-positive patients with DS-TB were less likely to access microbiological TB testing (57.0 vs. 64.8%, p<0.001) and were less likely to complete TB treatment (88.4% vs. 92.1%, p<0.001). This resulted in a lower overall proportion of HIV-positive patients compared to HIV-negative patients completing the TB care cascade (42.8% vs. 50.2%, p<0.001; **Table 2; Figures 1d and 1e**). For both HIV-positive and HIV-negative patients with DS-TB, the largest loss in the care cascade was due to patients not accessing microbiological TB testing resulting in 18,597 (range, 0-40,495; 75.2%) and 10,939 (range, 98-24,620; 70.6%) missed patients, respectively.

TB Diagnosis Trends from 2015 to 2018

Between 2015 and 2018 Xpert MTB/RIF was increasingly utilized as the first-line TB diagnostic tool in Zambia where 24,140 Xpert tests were sent for suspected pulmonary TB in 2015, which increased to 163,470 sent in 2018 (**Figure 2a**). During this same period, the number of sputum AFB smear microscopy investigations decreased from 95,300 in 2015 to 25,323 in 2018. While there was a small decrease in the absolute number of pulmonary TB cases diagnosed and notified in 2018 compared to 2015 (31,272 vs. 33,452), the proportion of microbiologically-confirmed TB cases that were notified during that period, substantially increased (56.0% [95CI, 55.5-56.6] vs. 44.1% [95%CI, 43.6-44.7]; **Figure 2a**). The scale-up of Xpert testing between 2015 and 2018 was also associated with a more than three-fold increase in the annual number of RR cases detected (627 vs. 196), and more than five-fold increase in the annual number of RR-TB cases that were notified and started on appropriate TB treatment (509 vs. 99; **Figure**

2b). During this period, there was a corresponding reduction in the proportion of RR-TB cases LTFU prior to the initiation of TB treatment from 49.5% in 2015 to 18.8% in 2018 (p<0.001).

TB Treatment Completion Trends from 2015 to 2018

Finally, we examined trends in the proportion of DS-TB patients who completed TB treatment once they were notified and initiated on therapy (**Figure 3**). Among new/relapse pulmonary TB cases, treatment completion rates steadily increased between 2015 and 2018 (86.2 [95%CI: 85.8-86.6] vs. 90.3% [95%CI: 90.0-90.7]; p<0.001). There was also a trend towards improved TB treatment completion rates from 2015 to 2018 among retreatment pulmonary TB cases (84.4% [95%CI: 83.3-85.5] vs. 87.2% [95%CI: 84.5-89.6]; p=0.06), however completion rates declined from 2017 to 2018 (95.0% [95%CI: 93.4-96.3] vs. 87.2% [95%CI: 84.5-89.6]; p<0.001). From 2015 to 2018, the proportion of patients with extrapulmonary TB completing TB treatment also improved (80.3% [95%CI: 79.4-81.1] vs. 87.8% [95%CI: 87.4-89.3]; p<0.001). The proportion of HIV-positive patients completing TB therapy did not meaningfully change from 2015 to 2018 (87.3% [95%CI: 86.9-87.7] vs. 88.4% [95%CI: 88.0-88.9]; p=0.001). Improvements in treatment completion rates from 2015 to 2018 were seen among patients who had a negative or unknown HIV status (82.4% [95%CI: 81.8-82.9] vs. 91.8% [95%CI: 91.4-92.2]; p<0.001) although, there was a small decline between 2017 and 2018 (93.7% [95%CI: 93.3-94.1] vs. 91.8% [95%CI:91.4-92.2]; p<0.001; **Figure 3**). In 2018, a lower proportion of HIV-positive TB patients completed therapy compared to HIV-negative patients (difference 3.4% [95%CI: 2.8-4.0]; p<0.001). Differences in the proportion of patients completing TB therapy according to HIV status were driven by a higher absolute number and proportion of cases that died or were LTFU during treatment among HIV-positive individuals compared to HIV-negative individuals (**Supplementary Table 1).**

Discussion

In this study we found that less than half of all TB cases in Zambia in 2018 were diagnosed with TB, initiated on TB treatment and completed therapy. We identified important losses at each step of the TB care cascade, however, we estimate that more than 40% of all individuals with TB in Zambia are not accessing microbiological TB testing – this accounted for nearly three-quarters of the estimated number of cases lost throughout the cascade. These results highlight

important research and programmatic priorities for improving TB care and TB-related outcomes in Zambia.

This represents the fourth national TB care cascade that has been characterized from a high burden TB country and builds upon similar analyses from South Africa, India, and Madagascar [7–9]. Our overall TB care cascade results are similar to those from these countries that each found that only about 50% of all TB patients were progressing through all steps of the care cascade and completing TB treatment. In India the largest losses in the care cascade were among those who did not access TB testing (28% of all cases) [7], in Madagascar the largest losses in the cascade were among those who were not diagnosed with TB despite seeking care and accessing a TB diagnostic facility (26% of all cases) [9], while in South Africa steady losses were seen prior to TB diagnosis (12% of all cases), prior to starting TB treatment (13% of all cases) and prior to successful completion of TB therapy (17% of all cases) [8]. In Zambia, 40% were estimated to have not accessed TB testing, while 4-5% of all TB cases were lost at each subsequent step of the care cascade. These differences highlight specific programmatic needs at different steps within the TB care cascade for each country and provides insight into the unique challenges that they each face.

Our results are consistent with several TB prevalence surveys suggesting that a large proportion of individuals with TB face barriers to healthcare seeking, barriers to accessing microbiological TB testing, or both [32,33]. Unfortunately, we are not able to discern whether the estimated 40% gap in patients not accessing TB microbiological investigations is predominantly driven by (a) individuals who fundamentally lacked access to primary health and TB facilities, (b) individuals who either delayed or never presented to TB testing facilities for evaluation of their illness, or (c) individuals who sought care at health facilities, but their illness was not suspected to be TB and thus they never had TB testing undertaken [34]. After onset of symptoms, individuals with undiagnosed TB may have long and complex journeys to TB care as they often face many barriers to care-seeking and accessing TB services (e.g., lack of knowledge, lack of social support, lack of time/finances, TB/HIV-related stigma, cultural and gender norms) [33,35,36]. In the last Zambian national TB prevalence survey conducted in 2013 and 2014, only 60% of previously undiagnosed individuals with TB were symptomatic, of whom 50% had sought care

for their illness at a health facility [12]. Furthermore, once patients do access healthcare services, their TB illness may be missed – this has been shown to be a common problem in recent standardized patient studies conducted in Kenya [37], India [38] , and China [39].

Collectively, this suggests that both community-based and facility-based active TB case finding strategies, as well as training of healthcare providers to improve recognition of and testing for TB, are likely to be important to activities to increase detection of individuals with TB in Zambia. Community-based active TB case finding may help overcome individuals' barriers to health-seeking and accessing TB services, possibly resulting in a greater absolute number of TB patients diagnosed and patients who are detected earlier [40–42]. However, effective and sustainable community-based active TB case finding strategies are not well-described and represent an urgent TB research need [33,43]. There is strong evidence demonstrating that facility-based, active TB case finding strategies are efficient and may yield a large number of cases that would otherwise have been missed, especially in high burden settings [44–47]. A recent study evaluating a multicomponent active TB case finding strategy in a high burden primary health care facility in Lusaka, Zambia found that total TB notifications increased by 35% during the intervention period; of the total TB cases, 91.5% were from facility-based case finding interventions while 8.5% were from community-based case finding interventions [47]. One important component of this strategy was the implementation of patient-friendly TB fast-track points at health facilities that improved access by allowing individuals with TB symptoms to skip the regular que and undergo rapid screening and testing for TB. Further research is needed to understand what potential strategies to improve TB care engagement and diagnosis are most preferred by and acceptable to community members in high-burden settings.

We estimate that nearly 10% of individuals diagnosed with TB were LTFU prior to the initiation of TB treatment. Pre-treatment LTFU is common in many high-burden settings as demonstrated by a systematic review that found that 4-38% (weighted proportion 18%) of TB patients in sub-Saharan Africa were lost at this step in the cascade [48]. This may be accounted for by patients who died prior to initiation of therapy – a common finding among such patients – and patients who cannot be traced after diagnosis either due to missing/incorrect contact information, or because they have moved away. A recent qualitative study among TB patients and health care

workers (HCW) in India provided further understanding of the factors that may contribute to LTFU prior to the initiation of TB therapy [49]. The authors identified challenges and constraints related to organizational and administrative barriers resulting in patient disengagement from TB services over frustration as well as negative HCW attitudes and behaviors resulting in patient distrust and feeling that their autonomy had been violated. There is an important need to design, evaluate and implement strategies that may address patient-level and health system factors and reduce pre-treatment LTFU [48]. It should be noted that pre-treatment loss-to-follow-up estimates may be overestimated because they fail to account for individuals who were in fact started on TB therapy but were not officially registered and therefore never notified to the NTP (under-notification). Zambia's NTP has recently completed a study to estimate the proportion of patients who are diagnosed but not notified as well as the proportion of those who are started on treatment but never reported. This study will yield improved estimates of pre-treatment loss-to-follow-up, which will allow for improved evaluations of programmatic changes that aim to improve TB diagnosis and linkage to TB treatment and care.

We found that important progress has been made in Zambia with regard to microbiological TB diagnosis and TB treatment completion from 2015 to 2018. During this period there was a massive effort to scale-up the availability of Xpert MTB/RIF as the first-line TB diagnostic for all forms of TB. This was associated with a 12% increase in the proportion of TB patients who were microbiologically-confirmed (2,692 additional annual drug-susceptibility patients). Importantly, because Xpert also provides rapid simultaneous detection of rifampicin-resistance, its scale-up was also associated with a three-fold increase in RR-TB patients detected and a five-fold increase in the number of RR-TB patients who were notified and started on TB treatment. Zambia is currently preparing to scale-up Xpert Ultra cartridges, which when paired with continued efforts to decentralize Xpert testing, should allow for further gains in the detection of HIV-associated TB, extra-pulmonary TB, and RR-TB [50]. There was also evidence of improved TB treatment completion rates for nearly all forms of TB between 2015 and 2018. While it is important to recognize progress that has been made, smaller but critically important gaps in the TB care cascade remain due to missed diagnoses and lack of treatment completion. Further efforts to expand access to microbiological TB testing and interventions to bolster TB treatment adherence that are grounded in person-centered care approaches - such as decentralization of

services coupled with improved education and communication as well as material and psychological support - are needed [51,52].

PLHIV accounted for 60% of DS-TB cases in Zambia and were more likely to be lost at several steps of the cascade compared to HIV-negative individuals. This finding emphasizes the need to strengthen HIV-TB collaborative activities [33,53]. Due to non-specific clinical presentations and radiographic findings, one of the most important challenges to improving HIV-associated TB outcomes remains TB diagnosis [54]. Non-specific symptoms may delay care-seeking among PLHIV, and without systematic TB screening among PLHIV presenting to and in-care, the diagnosis of many TB cases may be further delayed or missed. Systematic screening for TB at each clinical presentation [55] must be coupled with access to improved microbiological diagnostic tools such as Xpert Ultra [56] and urine LAM [56,57] testing to facilitate rapid TB detection and TB treatment initiation in order to minimize pre-treatment loss-to follow-up and improve clinical outcomes. Compared to HIV-negative patients, HIV-positive patients were less likely to complete TB therapy, and TB treatment completion rates among PLHIV did not significantly change over a four-year period from 2015 to 2018. Previously, a study among PLHIV in Zambia found that a large number of individuals LTFU from HIV services had died and that programmatic mortality rates were substantially under-reported [23]; this suggests that mortality among PLHIV LTFU from TB treatment services is high and that TB-related mortality among PLHIV in Zambia is likely underestimated. The implementation of tailored interventions to improve adherence to TB treatment [51,58] as well as antiretroviral therapy [59] among this highly vulnerable population therapy are needed.

Notably, we found that less than one quarter of RR-TB cases in 2018 were detected, started on appropriate treatment and completed appropriate therapy. This was despite improved access to rapid drug susceptibility via the scale-up of Xpert MTB/RIF testing from 2015 to 2018 and shorter and simplified drug-resistant TB regimens being introduced in 2018 [16]. The high rate of attrition of RR-TB patients throughout the care cascade argues for the need for specific investments in systems strengthening to improve drug resistant TB diagnosis and treatment in Zambia, mirroring this dire need in most high TB burden countries [19,33,60,61]. One important contributing factor to the large number of RR-TB patients not accessing DST is the high

proportion of patients who are being diagnosed clinically and/or on the basis of radiological findings only – this accounted for approximately 44% of pulmonary TB cases in Zambia in 2018. Notably, the scale-up of Xpert testing between 2015 to 2018 was associated with a more than 30% reduction in the proportion of RR-/MDR-TB cases that were LTFU after diagnosis and prior to initiation of treatment – this is likely due to the substantially faster detection of rifampicin resistance compared to conventional culture-based methods. Collectively, this demonstrates the importance of continued efforts to expand access to Xpert testing in Zambia in order to facilitate confirmation of TB diagnoses coupled with rapid detection of rifampicin resistance. While the implementation of existing diagnostic tools as well as improved DR-TB treatment regimens must be optimized, there remains a continued need for the development of rapid low-cost drug susceptibility testing (DST) that can be scaled-up to provide decentralized access to first- and second-line DST aligned with current treatment recommendations [62], as well as continued progress towards shorter, less toxic, and more effective DR-TB treatment regimens [63].

This study utilized a validated analysis method [6] incorporating a number of data sources to derive nationally representative estimates of the TB care cascade in Zambia; however, there were some limitations. As with other published TB cascades analyses, there is uncertainty around the estimates, especially the overall number of TB cases. The total burden of TB was calculated using indirect estimates from modelling that were based upon case notification data and a prior national TB prevalence survey. We derived a conservative estimate of the total TB burden that accounted for missed cases from the prior year [8] and that therefore may be a more appropriate estimate than measurements of TB incidence, which are rarely feasible to directly estimate [64]. Due to a lack of a unique national patient identifier, we were unable to link specific individuals with their outcomes as they progressed through the TB care cascade and thus unique individuals in one step of the cascade may differ from those in the following step; where possible, we attempted to account for duplicate diagnostic and treatment data, which was uncommon. Implementation of a unique TB patient identifier, and an improved TB data surveillance program with enhanced data integration would greatly improve future estimates and allow for real time individual-level, facility-level, and sub-national-level data to inform program strengthening.

Given the potential importance of gender to TB epidemiology [32,65] and potential differential health-seeking behaviors and access to TB services [36,66,67], we sought to characterize the TB care cascade among men and women. For example, the prevalence of TB among men in Zambia's first national TB prevalence survey in 2013/2014 was almost twice as high as that among women (833 vs. 487 cases per 100,000 persons) [12] and men with presumptive TB were less likely to have sought care for their symptoms than women (31.4% vs. 38.4%) [68]. Unfortunately, sex-disaggregated data sources were not available that would have allowed for each step of the cascade to be estimated. It is important that TB programs collect sex-disaggregated diagnostic and treatment data to help ensure equity in access and treatment benefits. Additionally, because incidence, diagnosis, notification and treatment numbers are from 2018, we feel our analysis accurately represents the national TB care cascade in 2018; however, pre-treatment LTFU estimates were informed by patient-level data from 2017 and the proportion of cases with rifampicin resistance were informed by higher-end estimates from the most recent national drug resistance survey conducted in 2008 [22]. An updated drug resistance survey is currently underway and will provide new estimates that will better guide programmatic priorities. Finally, to our knowledge, there are no locally or regionally-representative estimates of TB relapse rates after documented TB treatment completion. This is an important quality metric of individuals' adherence to therapy as well as TB treatment programs and should be assessed in future research studies [6].

In conclusion, in 2018 only 45% of individuals with TB in Zambia completed the TB care cascade, and most losses were among patients who never accessed TB testing. Additionally, only 22% of all RR-TB patients successfully completed appropriate TB treatment and HIV-positive patients had substantially worse TB outcomes compared to HIV-negative patients. Our results suggest that continued systems-strengthening coupled with patient-centered engagement strategies are required throughout the TB cascade of care, however, implementation of active TB case finding strategies coupled with a renewed focus on those with rifampicin-resistance and PLHIV are urgently needed to improve TB-related outcomes and TB control in Zambia.

Contributions

PL, ADK and MM conceived the study. PL, RC, AS and KM were responsible for project administration. CCK, JM, and SN collected and organized the data. ADK conducted the analysis and developed the figures with input from PL, MM, RS, MK, CCK, JM, SN, RC, AS, and KM. ADK, PL, and MM wrote the first draft of the manuscript. All authors contributed to interpretation of data and editing of the article and approved the final version of the manuscript before submission.

Ethics

Because this was a retrospective, population-level analysis without the use of any patient identifiers, the University of Zambia Biomedical Research Ethics Committee determined that this study met the criteria for exempt-status (REF. 001-02-21).

Patient and public involvement

Patients and the public were not involved in the design and conduct of this analysis. However, there are plans to disseminate the findings to TB communities through TB stakeholder meetings with neighborhood health committees, which includes former TB patients and other community TB advocates.

Funding

ADK was supported by the National Institute of Allergy and Infectious Diseases (Grant No T32 AI060530).

Disclaimer

The funding sources had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the manuscript for publication.

Data availability statement

All data relevant to this study are included in the article or uploaded as supplementary information.

Competing Interests

All authors declare no competing interests.

References

1 World Health Organization. The End TB Strategy. World Health Organization, Geneva; 2015.
2 World Health Organization. Global Tuberculosis Report 2020. World Health Organization, Geneva; 2020.
3 Centers for Disease Control. CDC in Zambia. Center for Disease Control and Prevention, Atlanta; 2017.
4 Medland NA, McMahon JH, Chow EP, *et al.* The HIV care cascade: a systematic review of data sources, methodology and comparability. *J Int Aids Soc* 2015;**18**:20634. doi:10.7448/ias.18.1.20634
5 Reid MJA, Goosby E. Lessons learned from the HIV care cascade can help End TB. *Int J Tuberc Lung Dis* 2017;**21**:245–6. doi:10.5588/ijtld.17.0027
6 Subbaraman R, Nathavitharana RR, Mayer KH, *et al.* Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLOS Med* 2019;**16**:e1002754-18. doi:10.1371/journal.pmed.1002754
7 Subbaraman R, Nathavitharana RR, Satyanarayana S, *et al.* The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002149-38. doi:10.1371/journal.pmed.1002149
8 Naidoo P, Theron G, Rangaka MX, *et al.* The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. *J Infect Dis* 2017;**216**:S702–13. doi:10.1093/infdis/jix335
9 Knoblauch AM, Lapierre SG, Randriamanana D, *et al.* Multidrug-resistant tuberculosis surveillance and cascade of care in Madagascar: a five-year (2012–2017) retrospective study. *BMC Med* 2020;**18**:173. doi:10.1186/s12916-020-01626-6
10 United Nations Population Fund. Zambia - Overview. United Nations Population Fund, Geneva; 2020.
11 Joint United Nations Programme on HIV/AIDS. Country factsheets - Zambia 2019. Joint United Nations Programme on HIV/AIDS, Geneva; 2020.
12 Kapata N, Chanda-Kapata P, Ngosa W, *et al.* The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013–2014. *PLOS ONE* 2016;**11**:e0146392-14. doi:10.1371/journal.pone.0146392
13 Zambian Ministry of Health. Underreporting of TB patients in Zambia. National TB and Leprosy Programme, Lusaka; 2019.
14 The National Tuberculosis and Leprosy Program. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in Zambia. 2017.
15 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. World Health Organization, Geneva; 2017.
16 Challenge TB. Rapid Scale-Up of New Drugs and Regimens for the Treatment of Drug-Resistant TB in Zambia. FHI 360 Zambia Office, Lusaka 2020.
17 Zambia Ministry of Health. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection: 2018.
18 World Health Organization. Global Tuberculosis Report 2018. World Health Organization, Geneva; 2018.
19 World Health Organization. Global Tuberculosis Report 2019. World Health Organization, Geneva; 2019.

20 Glaziou P, Sismanidis C, Dodd PJ, Zignol M, Floyd K. Methods used by WHO to estimate the global burden of TB disease. World Health Organization, Geneva; 2018.

21 World Health Organization. Tuberculosis data. https://www.who.int/teams/global-tuberculosis-programme/data

22 Kapata N, Mbulo G, Cobelens F, *et al.* The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health* 2015;**20**:1492–500. doi:10.1111/tmi.12581

23 Holmes CB, Sikazwe I, Sikombe K, *et al.* Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. *PLOS Med* 2018;**15**:e1002489. doi:10.1371/journal.pmed.1002489

24 Zambia Statistics Agency, Ministry of Health (MOH) Zambia, and ICF. 2019. Zambia Demographic and Health Survey 2018. Lusaka, Zambia, and Rockville, Maryland, USA: Zambia Statistics Agency, Ministry of Health, and ICF.

25 Horne DJ, Kohli M, Zifodya JS, *et al.* Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2019 Jun; 2019(6): CD009593. doi: 10.1002/14651858.CD009593.pub4

26 Boehme CC, Nicol MP, Nabeta P, *et al.* Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *The Lancet* 2011;**377**:1495–505. doi:10.1016/s0140

27 Steingart KR, Henry M, Ng V, *et al.* Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006;**6**:570–81. doi:10.1016/s1473-3099(06)70578-3

28 World Health Organization. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. World Health Organization, Geneva; 2016.

29 Tortoli E, Benedetti M, Fontanelli A, *et al.* Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Micro* 2002;**40**:607–10. doi:10.1128/jcm.40.2.607-610.2002

30 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. World Health Organization, Genevea; 2014.

31 Dye C. Breaking the law: tuberculosis disobeys Styblo's rule. *Bull World Health Organ* 2008;**86**:4–4. doi:10.2471/blt.07.049510

32 Horton KC, MacPherson P, Houben RMGJ, *et al.* Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLOS Med* 2016;**13**:e1002119. doi:10.1371/journal.pmed.1002119

33 Reid MJA, Arinaminpathy N, Bloom A, *et al.* Building a tuberculosis-free world: The Lancet Commission on tuberculosis. *Lancet* 2019;**393**:1331–84. doi:10.1016/s0140-6736(19)30024-8

34 Subbaraman R, Jhaveri T, Nathavitharana RR. Closing gaps in the tuberculosis care cascade: an action-oriented research agenda. *J Clin Tuberc Other Mycobact Dis* 2020;**19**:100144. doi:10.1016/j.jctube.2020.100144

35 Vries SG de, Cremers AL, Heuvelings CC, *et al.* Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. *Lancet Infect Dis* 2017;**17**:e128–43. doi:10.1016/s1473-3099(16)30531-x

36 Krishnan L, Akande T, Shankar AV, *et al.* Gender-Related Barriers and Delays in Accessing Tuberculosis Diagnostic and Treatment Services: A Systematic Review of Qualitative Studies. *Tuberc Res Treat* 2014;**2014**:1–14. doi:10.1155/2014/215059

37 Daniels B, Dolinger A, Bedoya G, *et al.* Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. *BMJ Glob Health* 2017;**2**:e000333. doi:10.1136/bmjgh-2017-000333

38 Kwan A, Daniels B, Saria V, *et al.* Variations in the quality of tuberculosis care in urban India: A cross-sectional, standardized patient study in two cities. *PLOS Med* 2018;**15**:e1002653. doi:10.1371/journal.pmed.1002653

39 Sylvia S, Xue H, Zhou C, *et al.* Tuberculosis detection and the challenges of integrated care in rural China: A cross-sectional standardized patient study. *PLOS Med* 2017;**14**:e1002405. doi:10.1371/journal.pmed.1002405

40 Kranzer K, Afnan-Holmes H, Tomlin K, *et al.* The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013;**17**:432–46. doi:10.5588/ijtld.12.0743

41 STOB TB Partnership. Finding the Missing People with TB in Communities. Stop TB Partnership, Geneva; 2018.

42 Marks GB, Nguyen NV, Nguyen PTB, *et al.* Community-wide Screening for Tuberculosis in a High-Prevalence Setting. *New Engl J Med* 2019;**381**:1347–57. doi:10.1056/nejmoa1902129

43 Kerkhoff AD, Muyoyeta M, Cattamanchi A. Community-wide Screening for Tuberculosis. *New Engl J Med* 2020;**382**:1185–6. doi:10.1056/nejmc1916666

44 Shapiro AE, Chakravorty R, Akande T, Lonnroth K, Golub JE. A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. World Health Organization, Geneva; 2013.

45 STOB TB Partnership. Intensified TB Case Finding at Facility Level. Stop TB Partnership, Geneva; 2018.

46 Hanrahan CF, Nonyane BAS, Mmolawa L, *et al.* Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). *PLOS Med* 2019;**16**:e1002796. doi:10.1371/journal.pmed.1002796

47 Kagujje M, Chilikutu L, Somwe P, *et al.* Active TB case finding in a high burden setting; comparison of community and facility-based strategies in Lusaka, Zambia. *PLOS ONE* 2020.

48 MacPherson P, Houben RM, Glynn JR, *et al.* Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bull World Health Organ* 2013;**92**:126–38. doi:10.2471/blt.13.124800

49 Thomas BE, Suresh C, Lavanya J, *et al.* Understanding pretreatment loss to follow-up of tuberculosis patients: an explanatory qualitative study in Chennai, India. *BMJ Glob Health* 2020;**5**:e001974. doi:10.1136/bmjgh-2019-001974

50 Dorman SE, Schumacher SG, Alland D, *et al.* Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis* 2018;**18**:76–84. doi:10.1016/s1473-3099(17)30691-6

51 Alipanah N, Jarlsberg L, Miller C, *et al.* Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLOS Med* 2018;**15**:e1002595. doi:10.1371/journal.pmed.1002595

52 World Health Organization. A patient-centered approach to TB care. World Health Organization, Geneva; 2018.

53 World Health Organization. WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders. World Health Organization, Geneva; 2012.

54 Kerkhoff AD, Cattamanchi A. Diagnosis of HIV-Associated Tuberculosis. In: Sereti I, Bisson GP, Meintjes G (eds) HIV and Tuberculosis: A Formidable Alliance. Springer, Cham. 2019; 127-159.

55 World Health Organization. WHO Consolidated Guidelines on Tuberculosis, Module 2: Systematic Screening for Tuberculosis Disease. World Health Organization, Geneva; 2021.

56 World Health Organization. WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. World Health Organization, Geneva; 2017.

57 World Health Organization. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV: policy update 2019. World Health Organization, Geneva; 2019.

58 Subbaraman R, Mondesert L de, Musiimenta A, *et al.* Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. *BMJ Glob Health.* 2018;**3**:e001018. doi:10.1136/bmjgh-2018-001018

59 Kanters S, Park JJH, Chan K, *et al.* Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017;**4**:e31–40. doi:10.1016/s2352-3018(16)30206-5

60 Dowdy DW, Theron G, Tornheim JA, *et al.* Drug-resistant tuberculosis in 2017: at a crossroads. *Lancet Respir Medicine* 2017;**5**:241–2. doi:10.1016/s2213-2600(17)30081-4

61 Dheda K, MD PTG, MMed PGM, *et al.* The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med.* 2017;**5**:291–360. doi:10.1016/s2213-2600(17)30079-6

62 World Health Organization. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. World Health Organization, Geneva; 2014.

63 Kendall EA, Sahu S, Pai M, *et al.* What will it take to eliminate drug-resistant tuberculosis? *Int J Tuberc Lung Dis* 2019;**23**:535–46. doi:10.5588/ijtld.18.0217

64 Stop TB Partnership. TB Impact Measurement. Stop TB Partnership, Geneva; 2012.

65 Horton KC, Sumner T, Houben RMGJ, *et al.* A Bayesian Approach to Understanding Sex Differences in Tuberculosis Disease Burden. *Am J Epidemiol* 2018;**187**:2431–8. doi:10.1093/aje/kwy131

66 Chikovore J, Hart G, Kumwenda M, *et al.* 'For a mere cough, men must just chew Conjex, gain strength, and continue working': the provider construction and tuberculosis care-seeking implications in Blantyre, Malawi. *Glob Health Action* 2015;**8**:26292. doi:10.3402/gha.v8.26292

67 Chikovore J, Hart G, Kumwenda M, *et al.* TB and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. *Int J Tuberc Lung Dis* 2017;**21**:26–33. doi:10.5588/ijtld.16.0925

68 Chanda-Kapata P, Kapata N, Masiye F, *et al.* Health Seeking Behaviour among Individuals with Presumptive Tuberculosis in Zambia. *PLOS ONE* 2016;**11**:e0163975-11. doi:10.1371/journal.pone.0163975

Figure Legend

Figure 1. The tuberculosis care cascade in Zambia in 2018 among: (a) all tuberculosis cases; (b) drug-susceptible cases; (c) rifampicin-resistant cases; (d) drug-susceptible cases among HIV-positive individuals; (e) drug-susceptible cases among HIV-negative individuals.

Figure 2. Diagnoses and notifications of (a) all forms of drug-susceptible pulmonary tuberculosis in Zambia between 2015 and 2018, and (b) drug-resistant tuberculosis in Zambia between 2015 and 2018.

Figure 3. Overview of drug-susceptible tuberculosis treatment outcomes in Zambia between 2015 and 2018, disaggregated according to tuberculosis-type. Shapes represent the proportion of patients completing tuberculosis treatment.

Supporting information

Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV status.

Table 1. Approach to and data sources for estimating each step of the tuberculosis care cascade in Zambia in 2018.

	Step 1. TB burden	Step 2. Accessed tests	Step 3. Diagnosed	Step 4. Notified and treated	Step 5. Successfully treated
All TB cases	WHO estimates of TB incidence in 2018 plus 50% of the number of undetected cases from 2017 [19,21].	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV status (informed by published reports [25–27]), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual level data from 4 Zambian provinces in 2017).	Back calculated from number of cases notified (step 4) and proportion of patients lost-to-follow-up (LTFU) prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 [unpublished]) and number of microbiologically confirmed DS PTB cases notified (informed by aggregated facility-level TB notification data from 2018 [unpublished]).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Add DS-TB and RR-TB cases successfully treated.
Rifampicin-resistant TB cases	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance (informed by most recent Zambia National TB drug resistance survey in 2008 [22]).	Back calculated from RR-TB cases diagnosed (step 3) on the basis of cases bacteriologically diagnosed, by test type and test sensitivity (informed by published reports [25,28,29]).	Exact value from aggregated facility-level TB laboratory data from 2018 (unpublished).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases, all cases	Overall TB burden minus RR-TB cases.	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV status (informed by published reports [25–27]), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual level data from 4 Zambian provinces in 2017).	Back calculated from number of DS-TB cases notified (step 4) and proportion of LTFU prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 [unpublished]) and number of microbiologically confirmed DS PTB cases notified (informed by aggregated facility-level TB notification data from 2018 [unpublished]).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases,	WHO 2019 analysis of DS-TB incidence in 2017 plus 50% of the number of undetected	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB	Back calculated from number of cases notified (step 4) and proportion of patients LTFU prior to initiation of TB therapy (pre-	Exact value from aggregated facility-level TB notification data from 2018	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (number successfully treated)

HIV-positive individuals	cases from 2018 [19,21].	cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated ([25,26]).	treatment LTFU assumed to be the same independent of HIV status).	adjusted for the proportion of patients without an HIV test. (unpublished).	adjusted for proportion of patients without an HIV test (unpublished).
Drug-susceptible TB cases, HIV-negative individuals	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals.	Total number of DS-TB cases who accessed TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals.	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals.	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified.	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated.

Table 2. Overview of the tuberculosis care cascade in Zambia in 2018 according to type.

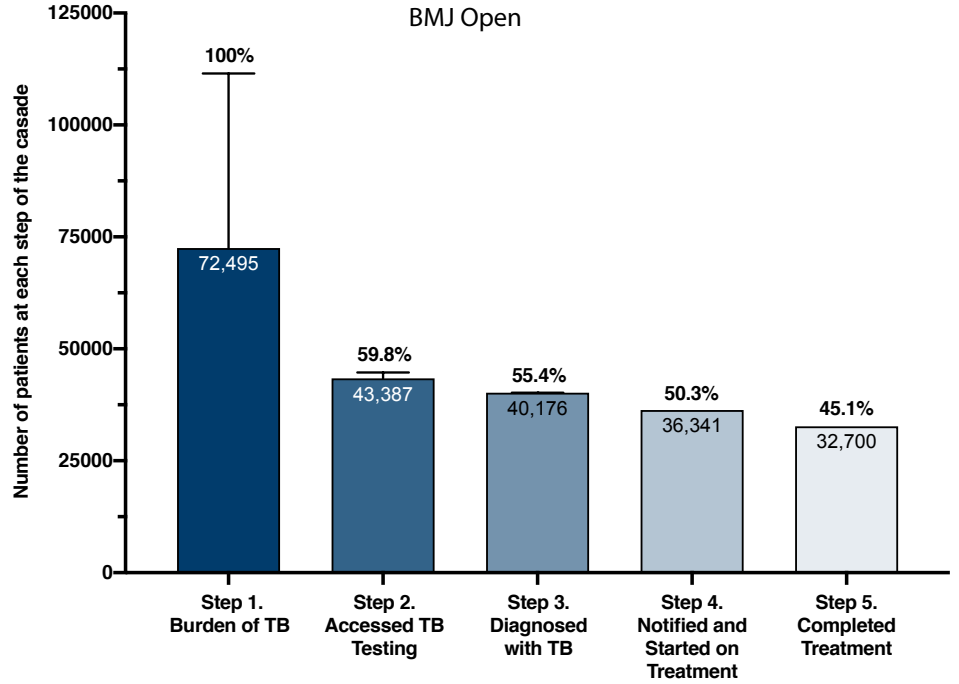
	Step 1. TB burden		Step 2. Accessed tests			Step 3. Diagnosed			Step 4. Notified and treated			Step 5. Successfully treated		
	Cases, range*	% of total burden^	Cases, range*	% of total burden^	% relative to prior step#	Cases, range*	% of total burden^	% relative to prior step#	Cases, range*	% of total burden^	% relative to prior step#	Cases, range*	% of total burden^	% relative to prior step#
Overall TB Cascade	72,495 (40,495-111,495)	100	43,387 (95%CI: 42,390-44,710)	59.8	59.8	40,176 (95%CI: 40,128-40,212)	55.4	92.6	36,431	50.2	90.7	32,700	45.1	89.8
Rifampin-resistant TB	1,740 (486-4,014)	100	910 (95%CI: 776-1,093)	52.3	52.3	627	36.0	68.9	509	29.3	81.2	396	22.8	77.8
Drug-susceptible TB, all	70,755 (40,009-107,481)	100	42,477 (95%CI: 41,614-43,625)	60.0	60.0	39,549 (95%CI: 39,501-39,585)	55.9	93.1	35,922	50.8	90.8	32,304	45.7	89.9
HIV-positive, drug-susceptible TB	43,411 (23,911-65,911)	100	24,746 (95%CI: 24,290-25,349)	57.0	57.0	23,133 (95%CI: 23,106-23,154)	53.3	93.5	21,012 (95%CI: 20,962-21,064)	48.4	90.8	18,579 (95%CI: 18,535-18,625)	42.8	88.4
HIV-negative, drug-susceptible TB	27,344 (16,098-41,570)	100	17,731 (95%CI: 17,324-18,276)	64.8	64.8	16,415 (95%CI: 16,395-16,431)	60.0	92.6	14,910 (95%CI: 14,858-14,960)	54.5	90.8	13,725 (95%CI: 13,679-13,769)	50.2	92.1

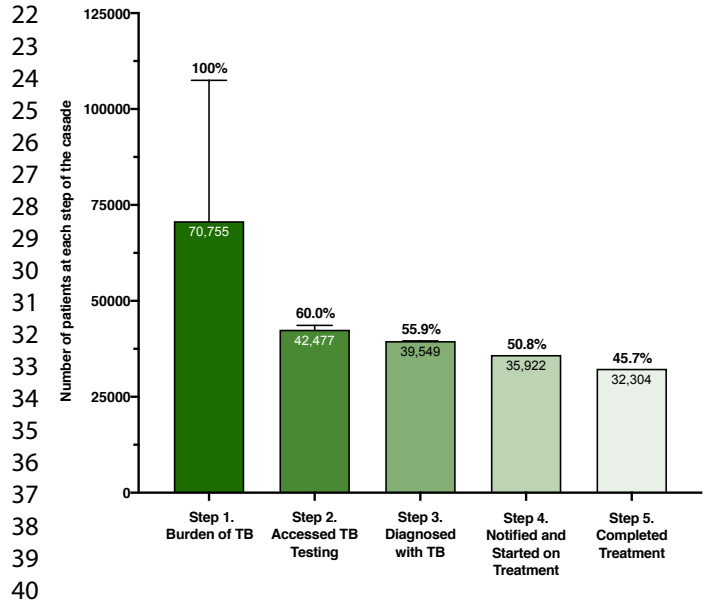
*Values in parentheses represent ranges, unless explicitly specified as 95% confidence intervals. ^Value represents the proportion of TB cases relative to the total TB burden (Step 1). #Value represents the proportion of TB cases relative to the prior step in the cascade.

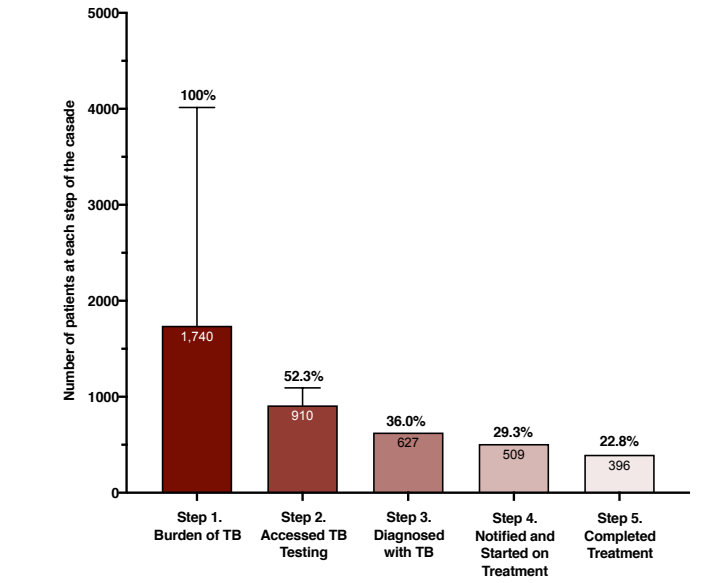
Table 3. Gap analysis of the tuberculosis care cascade in Zambia in 2018 according to type.

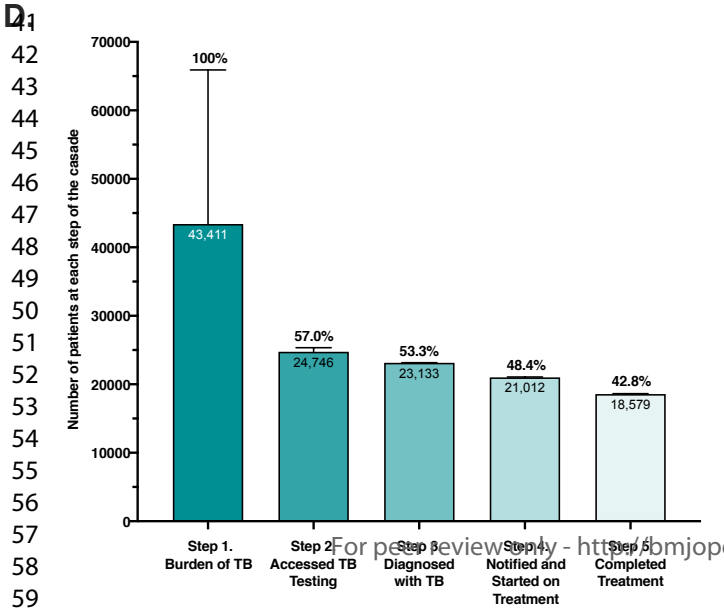
	Overall TB cases lost throughout the care cascade		Gap 1. Patient did not seek care at TB facility and/or have TB tests sent		Gap 2. TB tests sent, but TB missed		Gap 3. TB diagnosed but patient not started on TB treatment and/or not notified		Gap 4. TB treatment started, but not completed	
	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^	Cases, range*	Proportion (%)^
Overall TB Cascade	39,795 (8,191-79,191)	100	29,108 (0-66,777)	73.1	3,211 (95%CI: 2,262-4,506)	8.1	3,745 (95%CI: 3,697-3,781)	9.4	3,731	9.4
Rifampin-resistant TB	1,344 (486-4,014)	100	830 (0-2,921)	61.7	283# (95%CI: 149-466)	21.1	118	8.8	113	8.4
Drug-susceptible TB, all	38,451 (40,009-107,481)	100	28,278 (0-63,856)	73.5	2,928 (95%CI: 2,112-4,040)	7.6	3,627 (95%CI: 3,579-3,663)	9.4	3,618	9.4
HIV-positive, drug-susceptible TB	24,832 (5,376-47,286)	100	18,597 (0-40,495)	75.2	1,613 (95%CI: 1,185-2,194)	6.5	2,121 (95%CI: 2,094-2,142)	8.5	2,379 (95%CI: 2,337-2,529)	9.8
HIV-negative, drug-susceptible TB	13,619 (2,419-27,801)	100	10,939 (98-24,620)	70.6	1,315 (95%CI: 927-1,846)	9.7	1,505 (95%CI: 1,486-1,520)	11.1	1,239 (95%CI: 1,089-1,281)	8.7

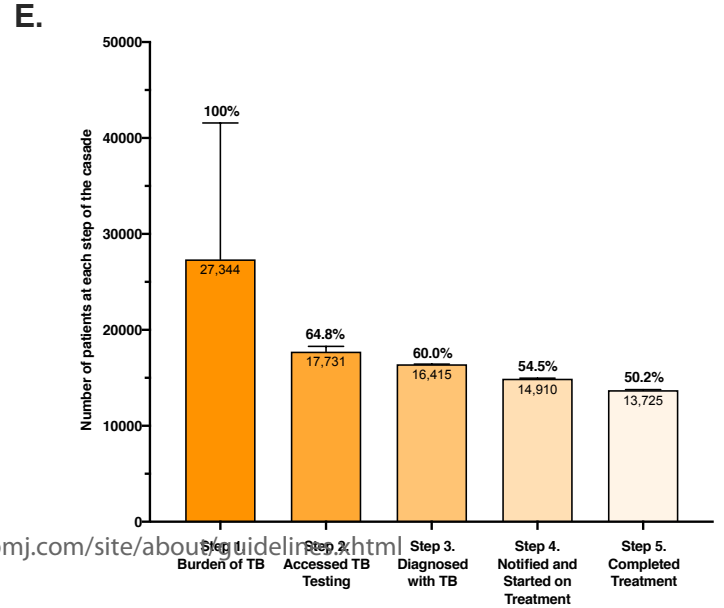
*Values in parentheses represent ranges, unless explicitly specified as 95% confidence intervals. ^Proportions are relative to the total number of TB cases estimated to have been lost throughout the care cascade. #For rifampicin resistant TB, either the TB diagnosis or the rifampicin resistance was missed.

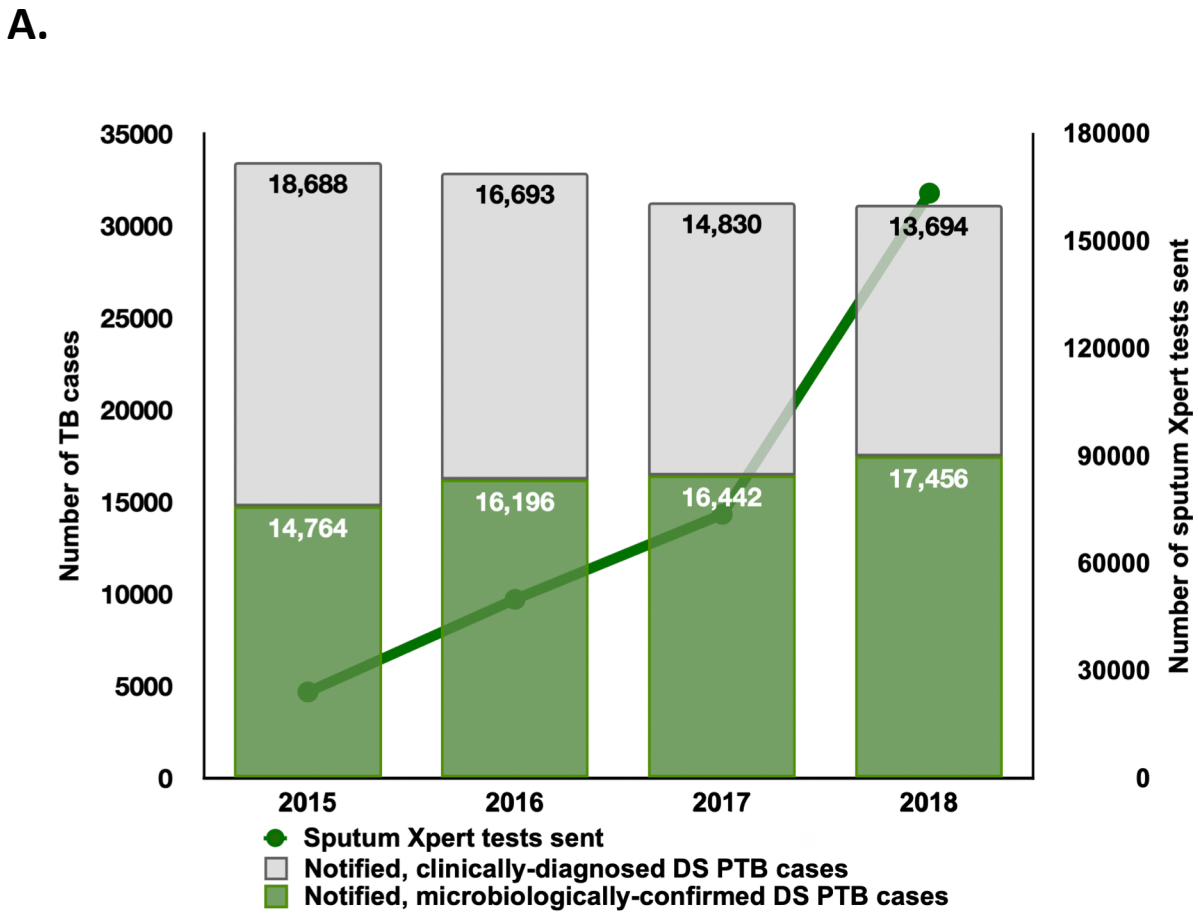


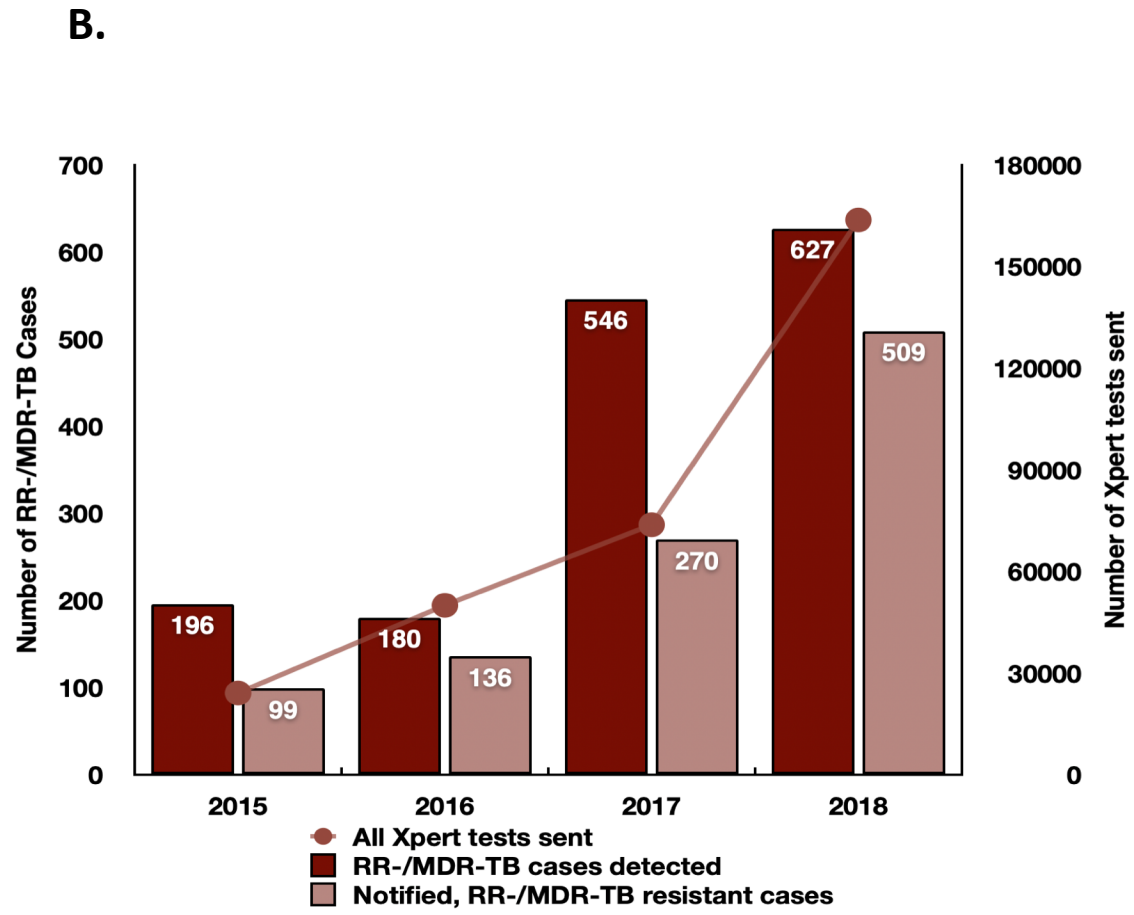


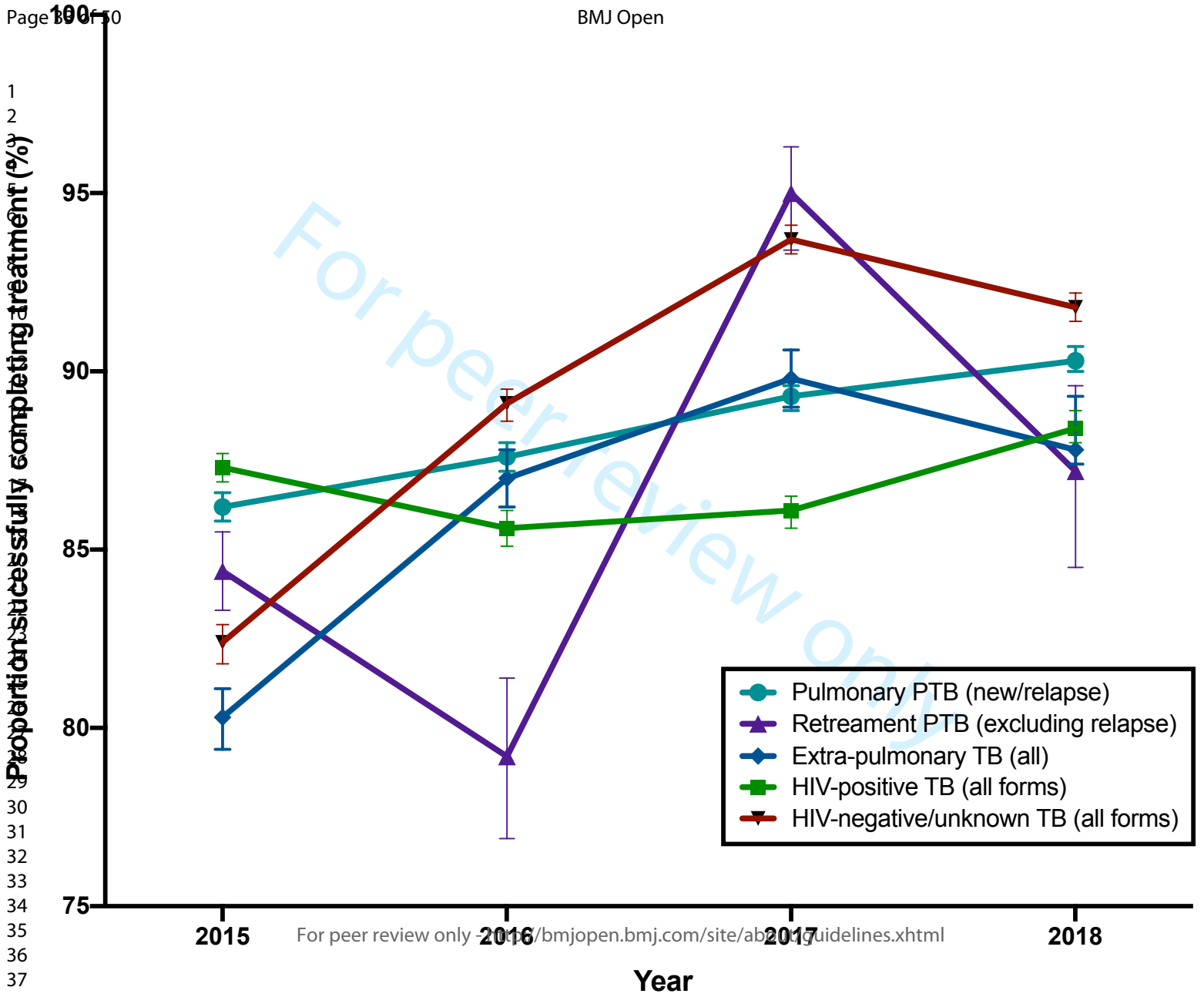







A.
35000
30000
25000
20000
15000
10000
5000
0
Number of TB cases
180000
150000
120000
90000
60000
30000
0
Number of sputum Xpert tests sent
18,688
16,693
14,830
13,694
14,764
16,196
16,442
17,456
2015
2016
2017
2018
Sputum Xpert tests sent
Notified, clinically-diagnosed DS PTB cases
Notified, microbiologically-confirmed DS PTB cases


B.
700
600
500
400
300
200
100
0
Number of RR-/MDR-TB Cases
180000
150000
120000
90000
60000
30000
0
Number of Xpert tests sent
196
99
180
136
546
270
627
509
2015
2016
2017
2018
All Xpert tests sent
RR-/MDR-TB cases detected
Notified, RR-/MDR-TB resistant cases



Supplementary Appendix. Estimation methods and calculations used to derive the tuberculosis care cascade in Zambia in 2018.

Table 1. Overall TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. TB burden	72,495 (40,495 - 111,495)	100	WHO 2019 analysis of TB incidence in 2018 plus 50% of the number of undetected cases from 2017.[1]	• TB incidence, 2018 (all): 60,000 • TB incidence, 2017 (all): 61,000 • Case detection rate, 2017: 59.0% • Estimated undetected cases 2017: 24,990 • 50% of undetected cases who have not died/self-cured: 12,495
Gap 1	29,108 (0-66,777)	40.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	43,387 (95%CI: 42,390-44,718)	59.8	Add DS-TB and RR-TB cases that accessed TB testing (see Tables 2 and 3 for estimates).	• DS-TB: 42,477 (95%CI: 41,614-43,625) • RR-TB: 910 (95%CI: 776-1,093)
Gap 2	3,211 (95%CI: 2,262-4,506)	4.4	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed	40,176 (95%CI: 40,128-40,212)	55.4	Add DS-TB and RR cases diagnosed (see Tables 2 and 3 for estimates).	• DS-TB: 39,549 (95%CI: 39,501-39,585) • RR-TB: 627
Gap 3	3,745 (95%CI: 3,697-3,781)	5.2	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated	36,431	50.2	Add DS-TB and RR cases notified and treated (see Tables 2 and 3 for estimates).	• DS-TB: 35,922 • RR-TB: 509
Gap 4	3,731	5.1	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated	32,700	45.1	Add DS-TB and RR cases successfully treated (see Tables 2 and 3 for estimates).	• DS-TB: 32,304 • RR-TB: 396

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 2a. Drug-susceptible TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	70,755 (40,009-107481)	100	Overall TB burden minus RR-TB cases.	• TB burden: 72,495 (40,495-111,495) • RR cases: 1740 (486-4014)
Gap 1	28,278 (0-63,856)	40.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	42,477 (95%CI: 41,614-43,625)	60.0	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based upon TB test sensitivity by HIV-status, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 39,549 (95%CI: 39,501-39,585) • Number missed: 2,928 (95%CI: 2,112-4,040)
Gap 2	2,928 (95%CI: 2,112-4,040)	4.1	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	39,549 (95%CI: 39,501-39,585)	55.9	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy. Pre-treatment LTFU estimated based on difference between number of microbiologically confirmed DS PTB cases detected and number of microbiologically confirmed DS PTB cases notified (Table 2c).	• Pre-treatment LTFU estimate: = 9.2 (95%CI: 9.1-9.3) • Number of patients notified in 2018: 35,922
Gap 3	3,627 (95%CI: 3,579-3,663)	5.1	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	35,922	50.8	Exact value from aggregated facility-level TB notification data.	• All patients with DS-TB who were notified and started on treatment (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).
Gap 4	3,618	5.1	Step 4 estimated cases minus Step 5 estimated cases	
Step 5. Successfully treated for TB.	32,304	45.7	Exact value from aggregated facility-level TB treatment outcomes data.	• All patients with DS-TB who successfully completed TB therapy (including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated cases).

Table 2b. Estimation method for determining number of patients with DS-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall
Total number of all microbiologically-confirmed TB cases (who therefore underwent microbiological tests)[1]	8,025 (PTB) + 320 (EPTB) = 8,345	9,803 (PTB)+1,137 (EPTB) = 10,940	19,285
Number of the above who underwent Xpert[1]	7,320	9,071	16,391
Number who underwent smear[1]	1,025	1,869	2,894
Proportion who underwent smear only (were smear-positive but Xpert either not done, or negative)[2]	96.9% (95%CI: 95.6-98.0)	98.1% (95%CI: 97.1-98.8)	97.7% (95%CI:96.9-98.3)
Number who underwent smear only	1,025 x .969% (95%CI: .956-.980) = 993 (95%CI: 980-1,005)	1,869 x .981% (95%CI: .971-.988) = 1,833 (95%CI: 1815-1,847)	-
Sensitivity of Xpert[3]	81% (95%CI 75-86)	88% (95%CI: 83-92)	85% (95%CI: 82-88)
Cases missed by Xpert	7,320/ .81 (95%CI .75-.86) - 7,320 = 1,717 (95CI: 1,192-2,440)	9,071 /.88 (95%CI: .83-.92)- 9,071 = 1,237 (95%CI: 789-1,858)	2,594 (95%CI: 1,980-4,298)
Sensitivity of smear microscopy[4,5]	50% (95%CI:42-57)	76% (95%CI: 70-80)	-
Cases missed by smear	993/0.50 (95%CI:0.42-0.57)- 993 = 1,025 (95%CI: 773-1,415)	1,833/0.76 (0.70-0.80)-1,833 = 590 (95%CI: 467-801)	1,615 (95%CI: 1,240-2,216)
Total combined cases missed by Xpert and smear	2,472 (95CI: 1,965-3,855)	1,827 (95%CI: 1,256-2,659)	4,569 (95%CI: 3,221-6,514)
Proportion of patients who had a negative Xpert that were empirically treated[2]	30.6% (95%CI: 28.6-32.7)	22.7% (95%CI:19.8-25.9)	28.9 (95%CI: 27.2-30.6)
Negative Xpert / received empiric therapy	1,717 (95CI: 1,192-2,440) x .306 (95%CI: .286-.327) = 525 (95: 341-798)	1,237 (95%CI: 789-1,858) x .227 (95%CI:.198-259) = 281 (95%CI: 156-481)	806 (95%CI: 497-1,279)

Proportion of patients who had a negative smear that were empirically treated[2]	58.9% (95%CI: 56.8-61.0)	39.2% (95%CI: 36.9-41.4)	50.1 (95%CI 48.5-51.6)
Negative smear / received empiric therapy	1,025 (95%CI: 773-1,415) x .589 (95%CI: .568-.610) = 604 (95%CI: 439-863)	590 (95%CI: 467-801) x .392% (95%CI: .369-.414) = 231 (95%CI: 172-332)	835 (95%CI: 612-1,195)
Total cases that were negative by Xpert or smear that were empirically treated	1,129 (95%CI: 780-1,661)	529 (95%CI: 329-813)	1,641 (95%CI: 1,109-2,474)
Total Missed cases (Total number of cases missed by Xpert or smear minus those were empirically treated)	1,613 (95%CI: 1,185-2,194)	1,315 (95%CI: 927-1,8460	2,928 (95%CI: 2,112-4,040)

[1]Exact value from 2018 national TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished), [3]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593.[4]Estimate from: Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 377:1495–505. [5]Estimate from: Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:570–81.

Table 2c. Estimation method for determining proportion of patients with pre-treatment lost-to-follow-up.

Variable	Overall
Unadjusted number of microbiologically-confirmed pulmonary TB cases[1]	19,285 (16,391 Xpert and 2,894 smear)
Proportion of patients with positive smear who also have a positive Xpert result[2]	2.3% (95%CI 1.7-3.1)
Number of patients with positive smear who also have a positive Xpert result[2]	2,894 x .023% (95%CI .017-.031) = 67 (95%CI: 49-90)
Adjusted number of microbiologically-confirmed PTB cases	(2,894 - 67 (95%CI: 49-90)) + 19,218 (95%CI: 19,195-19,236)
Number of patients with microbiologically-confirmed pulmonary TB notified in 2018[3]	17,456
Proportion of all patients with microbiologically-confirmed TB who were registered and started TB treatment	90.8 (95%CI: 90.7-90.9)
Pre-treatment lost-to-follow-up (LTFU) estimate:	100% - 90.8 (95%CI: 90.7-90.9) = 9.2% (95%CI: 9.1-9.3)

[1]Exact value from 2018 nationally aggregated TB laboratory register, [2]Estimate from: individual-level TB notification data from 4 provinces in 2017, n=11,814 (unpublished).[3]Exact value from 2018 nationally aggregated TB notification register.

Table 3. Rifampicin resistant TB Care Cascade in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	1,740 (486-4,014)	100	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance.	• TB burden: 72,495 (40,495-111,495) • Overall estimate of RR-TB: 2.4% (95CI: 1.2-3.6)[1]
Gap 1	830 (range, 0-2,921)	47.7	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	910 (95%CI: 776-1,093)	52.3	Back calculated from RR tuberculosis cases diagnosed on the basis of cases bacteriologically diagnosed, by test type and test sensitivity.	• RR-TB cases diagnosed: 627 • RR-TB cases missed: 283
Gap 2	283 (95%CI: 149-466)	16.3	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	627	36.0	Exact value from aggregated facility-level TB laboratory data.	• All patients with microbiologically-confirmed RR-TB
Gap 3	118	6.8	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	509	29.3	Exact value from aggregated facility-level TB notification data.	• All patients with RR-TB who were notified and started on treatment.
Gap 4	113	6.5	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	396	22.8	Exact value from aggregated facility-level TB treatment outcomes data.	• The number of RR-TB who were notified and started on treatment who were successfully treated.

[1]Estimate from: Kapata N, Mbulo G, Cobelens F, et al. The Second Zambian National Tuberculosis Drug Resistance survey - a comparison of conventional and molecular methods. *Trop Med Int Health*. 2015;20(11):1492-1500. This is the most recent Zambia national drug resistance survey. A higher estimate utilizing MDR-TB Plus chosen because it more closely coincides with WHO RR-TB incidence estimates for 2018.

Table 3b. Estimation method for determining number of patients with RR-TB who accessed TB testing in 2018

Variable	HIV-positive	HIV-negative	Overall, No
Number of laboratory-confirmed RR-cases	-	-	627
Proportion of RR-TB patients notified in 2018, by HIV-status.[1]	59.1% (95CI: 54.6-63.6)	40.9% (95%CI: 36.4-45.4)	-
Number of RR-TB patients diagnosed in 2018, by HIV-status	627 x 59.1% (95CI: 54.6-63.6) = 371 (95%CI: 342-399)	627 x 40.9% (95%CI: 36.4-45.4) = 256 (95%CI: 228-285)	627
Number of RR-cases detected by Xpert	-	-	372
Number of RR-cases detected by Xpert, by HIV-status	372 x 59.1% (95CI: 54.6-63.6) = 220 (95%CI: 203-237)	372 x 40.9% (95%CI: 36.4-45.4) = 152 (95%CI: 135-169)	372
Combined sensitivity of Xpert for Rif-Resistance, by HIV status[2]	• Sensitivity of Xpert for TB: 81% (95%CI: 75% to 86%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RR-TB: 77.8% (95%CI 70.5-83.4)	• Sensitivity of Xpert for TB: 88% (95%CI: 83% to 92%) • Sensitivity of Xpert for RIF-resistance: 96% (94% to 97%) • Overall sensitivity for RIF-resist TB: 84.5% (95%CI 78.0-89.2)	-
RR-cases missed by Xpert	220 (95%CI: 203-237)/ .778 (95%CI .705-.834) – 220 = 63 (95%CI: 24-116)	152 (95%CI: 135-169)/ .845 (95%CI .780-.892) – 152 = 28 (95%CI: 0-64)	91 (95%CI: 23-180)
Number of RR-cases detected by MDR-TB plus	-	-	135
Number of RR-cases detected by MDR-TB plus, by HIV-status	135 x 59.1% (95CI: 54.6-63.6) = 80 (95%CI: 74-86)	135 x 40.9% (95%CI: 36.4-45.4 = 55 (95%CI: 49-61)	135
Combined sensitivity of MDR-TB plus*[3]	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 48.5% (95%CI: 40.1-55.9)	• Sensitivity of smear for TB: 76% (95%CI: 70-80) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of MDR-TB plus: 96.9% (95CI%:95.5-98.0) • Overall sensitivity for RR-TB: 73.6% (95%CI: 66.9-78.4)	-
RR-cases missed by MDR-TB plus	80 (95%CI: 74-86) /.485 (95%CI: .401-.559) - 80 = 85 (95%CI: 52-134)	55 (95%CI: 49-61) / .736 (95%CI: .669-.784) - 55 = 20 (95%CI: 7-36)	105 (95%CI: 59-171)

Number of RR-cases detected by liquid culture (MGIT 960)*[4]			120
Number of RR-cases detected by liquid culture (MGIT 960)*[4], by HIV-status	120 x 59.1% (95CI: 54.6-63.6) = 71 (95%CI: 66-76)	120 x 40.9% (95%CI: 36.4-45.4 = 49 (95%CI: 44-54)	120
Combined sensitivity of liquid culture	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 49.6% (40.3-57.0)	• Sensitivity of smear for TB: 50% (95%CI:42-57) • Sensitivity of culture for smear-positive TB: 100% • Sensitivity of liquid culture for RR-TB: 99.2% (95%CI: 95.9-100) • Overall sensitivity for RR-TB: 75.4 (95%CI: 67.1-80.0)	-
RR-cases missed by liquid culture	71 (95%CI: 66-76) / .496 (95%CI: .403-.570) – 71 = 72 (95%CI: 61-83)	43 (95%CI: 49-54) / .754 (95%CI: .671-.800) – 43 = 16 (95%CI: 6-32)	88 (95%CI: 67-115)
Total microbiologically-missed cases	63 (95%CI: 24-116) + 85 (95%CI: 52-134) + 72 (95%CI: 61-83) = 220 (95%CI: 137-333)	28 (95%CI: 0-64) + 20 (95%CI: 7-36) + 16 (95%CI: 6-32) = 64 (95%CI: 13-133)	283 (95%CI: 149-466)
Received empiric therapy*	0	0	0
Total Missed cases	220 (95%CI: 137-333)	64 (95%CI: 13-133)	283 (95%CI: 149-466)

[1]Exact value from 2018 national TB laboratory register. [2]Estimate from: Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019 Jun 7;6(6):CD009593. [3]Estimate from: WHO. The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Geneva: WHO; 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/250586/9789241511261-eng.pdf?sequence=1, [4]Estimated from: Tortoli E, Benedetti M, Fontanelli A, Simonetti MT. Evaluation of automated BACTEC MGIT 960 system for testing susceptibility of Mycobacterium tuberculosis to four major antituberculous drugs: comparison with the radiometric BACTEC 460TB method and the agar plate method of proportion. *J Clin Microbiol*. 2002;40(2):607-610.

Table 4. Drug-susceptible TB Care Cascade among HIV-positive individuals in Zambia in 2018

Variable	Cases, range	Proportion (%), range	Estimation method	Calculation
Step 1. Overall TB burden	43,411 (23,911-65,911)	100	WHO 2019 analysis of TB incidence in 2017 plus 50% of the number of undetected cases from 2018.[1]	• TB incidence, 2018 (all): 36,000 (range, 23,000-51,000) • TB incidence, 2017 (all): 36,000 (range, 23,000-51,000) • Case detection rate, 2017: 58.8% (range, 41.5-92.1) • Estimated undetected cases 2017: 14,822 (range, 1,822-29,822) • 50% of undetected cases who have not died/self-cured: 7,411 (range, 911-14,911)
Gap 1	18,597 (0-40,495)	43.0	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	24,746 (95%CI: 24,290-25,349)	57.0	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based upon TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated (Table 2b).	• Number diagnosed: 23,133 (95CI: 23,106-23,154) • Number missed (table 2b): 1,613 (95%CI: 1,185-2,194)
Gap 2	1,613 (95%CI: 1,185-2,194)	3.7	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	23,133 (95%CI: 23,106-23,154)	53.3	Back calculated from number of cases notified and proportion of patients lost-to-follow-up prior to initiation of TB therapy [see Table 2c]; [assumed to be the same independent of HIV-status].	• Pre-treatment LTFU estimate: 9.2% (95%CI: 9.1-9.3) • Number of HIV-positive patients notified in 2018: 21,012 (95%CI: 20,962-21,064)
Gap 3	2,121 (95%CI: 2,094-2,142)	4.9	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	21,012 (95%CI: 20,962-21,064)	48.4	Exact value from aggregated facility-level TB notification data adjusted for proportion of patients without an HIV test.	• DS-TB: 19,332 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

Gap 4	2,433 (95%CI: 2,337-2,529)	5.6	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	18,579 (95%CI: 18,535-18,625)	42.8	Exact value from aggregated facility-level TB treatment outcomes data (number successfully treated) adjusted for proportion of patients without an HIV test.	• DS-TB: 17,624 • Proportion of all notified patients who had an HIV test: 94.9% (95%CI: 94.6-95.1)

[1]Estimate from: World Health Organization. Tuberculosis data. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.

Table 5. Drug-susceptible TB Care Cascade among HIV-negative individuals in Zambia in 2018

Variable	Cases, range	Proportion (%)	Estimation method	Calculation
Step 1. Overall TB burden	27,344 (16,098-41,570)	100	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals	• Number of DS-TB cases: 70,755 (range, 40,009-107,481) • Number of HIV-positive DS-TB cases: 43,411 (23,911-65,911)
Gap 1	10,939 (98-24,620)	35.2	Step 1 estimated cases minus Step 2 estimated cases.	
Step 2. Accessed tests	17,731 (95%CI: 17,324-18,276)	64.8	Total number of DS-TB cases who accesses TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals	• Number of DS-TB cases that accessed tests: 42,477 (95%CI: 41,614-43,625) • Number of HIV-positive DS-TB cases diagnosed: 24,746 (95%CI: 24,290-25,349)
Gap 2	1,315 (95%CI: 927-1,846)	4.8	Step 2 estimated cases minus Step 3 estimated cases.	
Step 3. Diagnosed with TB	16,415 (95%CI: 16,395-16,431)	60.0	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals	• Number of DS-TB cases diagnosed: 39,549 (95%CI: 39,501-39,585) • Number of HIV-positive DS-TB cases diagnosed: 23,133 (95%CI: 23,106-23,154)
Gap 3	1,505 (95%CI: 1,486-1,520)	5.5	Step 3 estimated cases minus Step 4 estimated cases.	
Step 4. Notified and treated for TB	14,910 (95%CI: 14,858-14,960)	54.5	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified	• Number of DS-TB cases notified: 35,922 • Number of HIV-positive DS-TB cases notified: 21,012 (95%CI: 20,962-21,064)
Gap 4	1,185 (95%CI: 1,089-1,281)	4.3	Step 4 estimated cases minus Step 5 estimated cases.	
Step 5. Successfully treated for TB	13,725 (95%CI: 13,679-13,769)	50.2	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated	• Number of DS-TB cases treated: 32,304 • Number of HIV-positive DS-TB cases treated: 18,633 (95%CI: 18,535-18,725)

Supplementary Table 1. Tuberculosis treatment outcomes in Zambia between 2015 and 2018 according to HIV-status.

	HIV-positive						HIV-negative or unknown HIV status					
	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated	Total treatment cohort	Completed treatment	Failed treatment	Died during treatment	LTFU during treatment	Not evaluated
2015	20967	18312 (87.3)	71 (0.3)	1117 (5.3)	682 (3.3)	785 (3.7)	20621	16986 (82.4)	102 (0.5)	1392 (6.8)	1168 (5.7)	973 (4.7)
2016	21655	18541 (85.6)	171 (0.8)	1354 (6.3)	705 (3.3)	884 (4.1)	18498	16481 (89.1)	55 (0.3)	1058 (5.7)	486 (2.6)	418 (2.3)
2017	20362	17527 (86.1)	136 (0.7)	1622 (8.0)	731 (3.6)	346 (1.7)	16841	15779 (93.7)	40 (0.2)	569 (3.4)	135 (0.8)	318 (1.9)
2018	19932	17624 (88.4)	113 (0.6)	1253 (6.3)	521 (2.6)	421 (2.1)	15990	14680 (91.8)	46 (0.3)	745 (4.7)	342 (2.1)	177 (1.1)

	Item No	Recommendation	Response:
Title and abstract			
	1	a) Indicate the study's design with a commonly used term in the title or the abstract	The design is included in the study title – **"The tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis" [p1].**
		b) Provide in the abstract an informative and balanced summary of what was done and what was found	This is provided (***see abstract [p2].***
Introduction			
Background	2	Explain the scientific background and rationale for the investigation being reported	This is described in the background section (see ***Background section paragraphs 2 and 3 [p4]).***
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific objectives are stated in the background section (see ***Background section paragraph 3 [p4]).***
Methods			
Study design	4	Present key elements of study design early in the paper	This is provided (***see Methods Section, paragraph 1 [p5]).***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up and data collection	This is provided (***see Methods Section, Setting and TB cascade data sources sub-sections [p5-7]).***
Participants	6	a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	This is provided (***see Methods Section, paragraph 1 [p5], and TB cascade data sources sub-section[p5-6]*****).**
		b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable.

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria if applicable	Outcomes, potential confounders and effect modifiers are described in detail (***see Methods Section, TB cascade estimation methods sub-section [p7-8]).***
Data sources/ measurements	8	For each variable of interest, give sources of data and details of methods of assessment. Describe comparability of assessment methods if there is more than one group	All data sources and methods of obtainment for variables of interest are described in detail (***see Methods Section, TB cascade estimation methods sub-section [p7-8], Table 1 and the Supplementary Appendix).***
Bias	9	Describe any efforts to address potential sources of bias	There are a few potential sources of bias that we discuss. One is the use of routine medical records, which may be incompletely documented. A second is that this analysis does not represent a cohort of individuals followed through each step of the care cascade; thus, different individuals may be captured at each step of the cascade. We also acknowledge that there is uncertainty around estimates (especially, TB incidence and incidence of rifampicin-resistance TB). These are discussed in detail (see ***Methods Section, TB cascade data sources sub-section [p6-7] and Discussion – paragraphs 9 and 10 [p18-19]).***
Study size	10	Explain how the study size was arrived at	We sought to include all persons with TB living in Zambia in 2018 (overall TB burden). We provide detailed information regarding how the total TB burden was calculated (***TB cascade estimation methods sub-section [p7-9]).***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	The analysis approach for all estimates is clearly detailed (***see Methods Section, TB cascade estimation methods sub-section [p7-9], Table 1 and the Supplementary Appendix).***

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	These details are provided in the methods section (***see Methods Section, TB cascade estimation methods sub-section, Table 1 and the Supplementary Appendix).***
		(b) Describe any methods used to examine subgroups and interactions	These details are provided in the methods section (***see Methods Section, TB cascade estimation methods sub-section [p7-9], Table 1 and the Supplementary Appendix).***
		(c) Explain how missing data were addressed	For the purposes of this analysis, data was assumed to be accurate and complete. This is described in the methods section (***see Methods Section, paragraph 1, and TB cascade data sources sub-section [p9]*).**
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable; estimating the number and proportion of patients lost-to-follow-up between each step of the TB care cascade was central to the study design (***see Methods Section, TB cascade estimation methods sub-section p7-9], Table 1 and the Supplementary Appendix and also Table 3).***
		(e) Describe any sensitivity analyses	No sensitivity analyses were conducted.
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This information is described in results section (***See Results section [p11], Table 2 and Figure 1).***
		(b) Give reasons for non-participation at each stage	Not directly applicable. The number of individuals reaching each step of the cascade and that are lost throughout the cascade are characterized in detail (***See Results section [p11-12], Tables 2 and 3).***
		(c) Consider use of a flow diagram	Not directly applicable. The TB care cascade summarizing the number of individuals reaching step of the care cascade is characterized in detail (***See Results section [p11-12], Figure 1).***

Descriptive Data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	This information is provided in the results section (***See Results section [p11-12], Table 2)***
		(b) Indicate number of participants with missing data for each variable of interest	This does not apply. All data were assumed to be accurate and complete (***see 12c above***).
		(c) Summarise follow-up time (eg, average and total amount)	This does not apply.
Outcome data	15	Report numbers of outcome events or summary measures over time	For the main analysis, summary measures are restricted to a single year (2018) and are summarized in the results section (***See Results section [p11-12], Table 2 and Figure 1).*** For TB diagnostic and treatment outcomes between 2015 and 2018 these are also summarized in the results section ***(See Results section, sub-sections TB Diagnosis Trends from 2015 to 2018 [p12-13] and TB Treatment Completion Trends from 2015 to 2018 [p13] and as well as corresponding Figures 2 and 3).***
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	All analyses presented are unadjusted. Estimates were determined both overall and disaggregated by HIV status and TB drug-susceptibility status (***See Results section [p11-13], Tables 1-3 and Figures 1-3).***
		(b) Report category boundaries when continuous variables were categorized	This does not apply as no continuous variable were categorized.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	This does not apply.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	We present all analyses (including disaggregated analyses) (***see results section [p11-13]).***
Discussion			
Key Results	18	Summarise key results with reference to study objectives	Our discussion section summarizes key results with reference to the study objectives defined in the final paragraph of the background section (***see Discussion Section [p13-19])***.

	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	We provide a discussion on limitations and potential sources of bias *(see Discussion Section, paragraphs 9 and 10 [p18-19]).*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	We have attempted to provide a conservative interpretation of our study results in the Discussion section and where appropriate linked our results to other published studies *(see Discussion Section [p13-19])*
Generalisability	21	Discuss the generalisability (external validity) of the study results	This is described *(see Discussion Section, paragraph 10 [p18-19]).*
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	This is described (*see section Funding section [p20]).*